

THE OFFICIAL  
PARENT'S SOURCEBOOK  
*on*

PRIMARY  
IMMUNODEFICIENCY



JAMES N. PARKER, M.D.  
AND PHILIP M. PARKER, PH.D., EDITORS

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ICON Health Publications  
 ICON Group International, Inc.  
 4370 La Jolla Village Drive, 4th Floor  
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## Dedication

To the healthcare professionals dedicating their time and efforts to the study of primary immunodeficiency.

## Acknowledgements

The collective knowledge generated from academic and applied research summarized in various references has been critical in the creation of this sourcebook which is best viewed as a comprehensive compilation and collection of information prepared by various official agencies which directly or indirectly are dedicated to primary immunodeficiency. All of the *Official Parent's Sourcebooks* draw from various agencies and institutions associated with the United States Department of Health and Human Services, and in particular, the Office of the Secretary of Health and Human Services (OS), the Administration for Children and Families (ACF), the Administration on Aging (AOA), the Agency for Healthcare Research and Quality (AHRQ), the Agency for Toxic Substances and Disease Registry (ATSDR), the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Healthcare Financing Administration (HCFA), the Health Resources and Services Administration (HRSA), the Indian Health Service (IHS), the institutions of the National Institutes of Health (NIH), the Program Support Center (PSC), and the Substance Abuse and Mental Health Services Administration (SAMHSA). In addition to these sources, information gathered from the National Library of Medicine, the United States Patent Office, the European Union, and their related organizations has been invaluable in the creation of this sourcebook. Some of the work represented was financially supported by the Research and Development Committee at INSEAD. This support is gratefully acknowledged. Finally, special thanks are owed to Tiffany LaRochelle for her excellent editorial support.

## About the Editors

### **James N. Parker, M.D.**

Dr. James N. Parker received his Bachelor of Science degree in Psychobiology from the University of California, Riverside and his M.D. from the University of California, San Diego. In addition to authoring numerous research publications, he has lectured at various academic institutions. Dr. Parker is the medical editor for the *Official Parent's Sourcebook* series published by ICON Health Publications.

### **Philip M. Parker, Ph.D.**

Philip M. Parker is the Eli Lilly Chair Professor of Innovation, Business and Society at INSEAD (Fontainebleau, France and Singapore). Dr. Parker has also been Professor at the University of California, San Diego and has taught courses at Harvard University, the Hong Kong University of Science and Technology, the Massachusetts Institute of Technology, Stanford University, and UCLA. Dr. Parker is the associate editor for the *Official Parent's Sourcebook* series published by ICON Health Publications.

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4370 La Jolla Village Drive, Fourth Floor  
San Diego, CA 92122 USA  
Fax: 858-546-4341  
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## INTRODUCTION

### Overview

Dr. C. Everett Koop, former U.S. Surgeon General, once said, “The best prescription is knowledge.”<sup>1</sup> The Agency for Healthcare Research and Quality (AHRQ) of the National Institutes of Health (NIH) echoes this view and recommends that all parents incorporate education into the treatment process. According to the AHRQ:

Finding out more about your [child’s] condition is a good place to start. By contacting groups that support your [child’s] condition, visiting your local library, and searching on the Internet, you can find good information to help guide your decisions for your [child’s] treatment. Some information may be hard to find—especially if you don't know where to look.<sup>2</sup>

As the AHRQ mentions, finding the right information is not an obvious task. Though many physicians and public officials had thought that the emergence of the Internet would do much to assist parents in obtaining reliable information, in March 2001 the National Institutes of Health issued the following warning:

The number of Web sites offering health-related resources grows every day. Many sites provide valuable information, while others may have information that is unreliable or misleading.<sup>3</sup>

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<sup>1</sup> Quotation from <http://www.drkoop.com>.

<sup>2</sup> The Agency for Healthcare Research and Quality (AHRQ):  
<http://www.ahrq.gov/consumer/diaginfo.htm>.

<sup>3</sup> From the NIH, National Cancer Institute (NCI):  
<http://cancertrials.nci.nih.gov/beyond/evaluating.html>.

Since the late 1990s, physicians have seen a general increase in parent Internet usage rates. Parents frequently enter their children's doctor's offices with printed Web pages of home remedies in the guise of latest medical research. This scenario is so common that doctors often spend more time dispelling misleading information than guiding children through sound therapies. *The Official Parent's Sourcebook on Primary Immunodeficiency* has been created for parents who have decided to make education and research an integral part of the treatment process. The pages that follow will tell you where and how to look for information covering virtually all topics related to primary immunodeficiency, from the essentials to the most advanced areas of research.

The title of this book includes the word "official." This reflects the fact that the sourcebook draws from public, academic, government, and peer-reviewed research. Selected readings from various agencies are reproduced to give you some of the latest official information available to date on primary immunodeficiency.

Given parents' increasing sophistication in using the Internet, abundant references to reliable Internet-based resources are provided throughout this sourcebook. Where possible, guidance is provided on how to obtain free-of-charge, primary research results as well as more detailed information via the Internet. E-book and electronic versions of this sourcebook are fully interactive with each of the Internet sites mentioned (clicking on a hyperlink automatically opens your browser to the site indicated). Hard copy users of this sourcebook can type cited Web addresses directly into their browsers to obtain access to the corresponding sites. Since we are working with ICON Health Publications, hard copy *Sourcebooks* are frequently updated and printed on demand to ensure that the information provided is current.

In addition to extensive references accessible via the Internet, every chapter presents a "Vocabulary Builder." Many health guides offer glossaries of technical or uncommon terms in an appendix. In editing this sourcebook, we have decided to place a smaller glossary within each chapter that covers terms used in that chapter. Given the technical nature of some chapters, you may need to revisit many sections. Building one's vocabulary of medical terms in such a gradual manner has been shown to improve the learning process.

We must emphasize that no sourcebook on primary immunodeficiency should affirm that a specific diagnostic procedure or treatment discussed in a research study, patent, or doctoral dissertation is "correct" or your child's best option. This sourcebook is no exception. Each child is unique. Deciding

on appropriate options is always up to parents in consultation with their children's physicians and healthcare providers.

## Organization

This sourcebook is organized into three parts. Part I explores basic techniques to researching primary immunodeficiency (e.g. finding guidelines on diagnosis, treatments, and prognosis), followed by a number of topics, including information on how to get in touch with organizations, associations, or other parent networks dedicated to primary immunodeficiency. It also gives you sources of information that can help you find a doctor in your local area specializing in treating primary immunodeficiency. Collectively, the material presented in Part I is a complete primer on basic research topics for primary immunodeficiency.

Part II moves on to advanced research dedicated to primary immunodeficiency. Part II is intended for those willing to invest many hours of hard work and study. It is here that we direct you to the latest scientific and applied research on primary immunodeficiency. When possible, contact names, links via the Internet, and summaries are provided. It is in Part II where the vocabulary process becomes important as authors publishing advanced research frequently use highly specialized language. In general, every attempt is made to recommend "free-to-use" options.

Part III provides appendices of useful background reading covering primary immunodeficiency or related disorders. The appendices are dedicated to more pragmatic issues facing parents. Accessing materials via medical libraries may be the only option for some parents, so a guide is provided for finding local medical libraries which are open to the public. Part III, therefore, focuses on advice that goes beyond the biological and scientific issues facing children with primary immunodeficiency and their families.

## Scope

While this sourcebook covers primary immunodeficiency, doctors, research publications, and specialists may refer to your child's condition using a variety of terms. Therefore, you should understand that primary immunodeficiency is often considered a synonym or a condition closely related to the following:

- Acquired Hypogammaglobulinemia

- Common Variable Hypogammaglobulinemia
- Immunosuppression
- Late-onset Immunoglobulin Deficiency

In addition to synonyms and related conditions, physicians may refer to primary immunodeficiency using certain coding systems. The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) is the most commonly used system of classification for the world's illnesses. Your physician may use this coding system as an administrative or tracking tool. The following classification is commonly used for primary immunodeficiency:<sup>4</sup>

- 279.3 immunity deficiency, unspecified

For the purposes of this sourcebook, we have attempted to be as inclusive as possible, looking for official information for all of the synonyms relevant to primary immunodeficiency. You may find it useful to refer to synonyms when accessing databases or interacting with healthcare professionals and medical librarians.

## Moving Forward

Since the 1980s, the world has seen a proliferation of healthcare guides covering most illnesses. Some are written by parents, patients, or their family members. These generally take a layperson's approach to understanding and coping with an illness or disorder. They can be uplifting, encouraging, and highly supportive. Other guides are authored by physicians or other healthcare providers who have a more clinical outlook. Each of these two styles of guide has its purpose and can be quite useful.

As editors, we have chosen a third route. We have chosen to expose you to as many sources of official and peer-reviewed information as practical, for the purpose of educating you about basic and advanced knowledge as recognized by medical science today. You can think of this sourcebook as your personal Internet age reference librarian.

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<sup>4</sup> This list is based on the official version of the World Health Organization's 9th Revision, International Classification of Diseases (ICD-9). According to the National Technical Information Service, "ICD-9CM extensions, interpretations, modifications, addenda, or errata other than those approved by the U.S. Public Health Service and the Health Care Financing Administration are not to be considered official and should not be utilized. Continuous maintenance of the ICD-9-CM is the responsibility of the federal government."

Why “Internet age”? When their child has been diagnosed with primary immunodeficiency, parents will often log on to the Internet, type words into a search engine, and receive several Web site listings which are mostly irrelevant or redundant. Parents are left to wonder where the relevant information is, and how to obtain it. Since only the smallest fraction of information dealing with primary immunodeficiency is even indexed in search engines, a non-systematic approach often leads to frustration and disappointment. With this sourcebook, we hope to direct you to the information you need that you would not likely find using popular Web directories. Beyond Web listings, in many cases we will reproduce brief summaries or abstracts of available reference materials. These abstracts often contain distilled information on topics of discussion.

While we focus on the more scientific aspects of primary immunodeficiency, there is, of course, the emotional side to consider. Later in the sourcebook, we provide a chapter dedicated to helping you find parent groups and associations that can provide additional support beyond research produced by medical science. We hope that the choices we have made give you and your child the most options in moving forward. In this way, we wish you the best in your efforts to incorporate this educational approach into your child’s treatment plan.

*The Editors*





## **PART I: THE ESSENTIALS**

### **ABOUT PART I**

Part I has been edited to give you access to what we feel are “the essentials” on primary immunodeficiency. The essentials typically include a definition or description of the condition, a discussion of who it affects, the signs or symptoms, tests or diagnostic procedures, and treatments for disease. Your child’s doctor or healthcare provider may have already explained the essentials of primary immunodeficiency to you or even given you a pamphlet or brochure describing the condition. Now you are searching for more in-depth information. As editors, we have decided, nevertheless, to include a discussion on where to find essential information that can complement what the doctor has already told you. In this section we recommend a process, not a particular Web site or reference book. The process ensures that, as you search the Web, you gain background information in such a way as to maximize your understanding.



## **CHAPTER 1. THE ESSENTIALS ON PRIMARY IMMUNODEFICIENCY: GUIDELINES**

### **Overview**

Official agencies, as well as federally-funded institutions supported by national grants, frequently publish a variety of guidelines on primary immunodeficiency. These are typically called “Fact Sheets” or “Guidelines.” They can take the form of a brochure, information kit, pamphlet, or flyer. Often they are only a few pages in length. The great advantage of guidelines over other sources is that they are often written with the parent in mind. Since new guidelines on primary immunodeficiency can appear at any moment and be published by a number of sources, the best approach to finding guidelines is to systematically scan the Internet-based services that post them.

### The National Institutes of Health (NIH)<sup>5</sup>

The National Institutes of Health (NIH) is the first place to search for relatively current guidelines and fact sheets on primary immunodeficiency. Originally founded in 1887, the NIH is one of the world's foremost medical research centers and the federal focal point for medical research in the United States. At any given time, the NIH supports some 35,000 research grants at universities, medical schools, and other research and training institutions, both nationally and internationally. The rosters of those who have conducted research or who have received NIH support over the years include the world's most illustrious scientists and physicians. Among them are 97 scientists who have won the Nobel Prize for achievement in medicine.

There is no guarantee that any one Institute will have a guideline on a specific medical condition, though the National Institutes of Health collectively publish over 600 guidelines for both common and rare disorders. The best way to access NIH guidelines is via the Internet. Although the NIH is organized into many different Institutes and Offices, the following is a list of key Web sites where you are most likely to find NIH clinical guidelines and publications dealing with primary immunodeficiency and associated conditions:

- Office of the Director (OD); guidelines consolidated across agencies available at **<http://www.nih.gov/health/consumer/conkey.htm>**
- National Library of Medicine (NLM); extensive encyclopedia (A.D.A.M., Inc.) with guidelines available at **<http://www.nlm.nih.gov/medlineplus/healthtopics.html>**
- National Institute of Child Health and Human Development (NICHD); guidelines available at **<http://www.nichd.nih.gov/publications/pubskey.cfm>**

Among those listed above, the National Institute of Child Health and Human Development (NICHD) is especially noteworthy. The mission of the NICHD, a part of the National Institutes of Health (NIH), is to support and conduct research on topics related to the health of children, adults, families, and populations. NICHD research focuses on the idea that events that happen prior to and throughout pregnancy as well as during childhood have a great impact on the health and well-being of adults. The following

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<sup>5</sup> Adapted from the NIH: **<http://www.nih.gov/about/NIHoverview.html>**.

guideline is one the NICHD provides concerning primary immunodeficiency.<sup>6</sup>

## **What Is Primary Immunodeficiency (PI)?<sup>7</sup>**

Most of us are no strangers to infections. Just about everybody has had colds and coughs and infected cuts, the flu or chicken pox. Some people have had first-hand experience with infections that are even more serious—pneumonia and meningitis.

Usually, we expect to recover quickly from an infection. We count on our body's immune defenses (sometimes with the help of antibiotics) to get rid of any germs that cause infection, and to protect us against new germs in the future.

Some people, however, are born with an immune defense system that is faulty. They are missing some or, in the worst cases, almost all of the body's immune defense weapons. Such people are said to have a primary immunodeficiency (PI).

There are over 70 different types of PIs. Each type has somewhat different symptoms, depending on which parts of the immune defense system are deficient. Some deficiencies are deadly, while some are mild. But they all have one thing in common: they may open the door to multiple infections.

Individuals with PI—many of them infants and children—get one infection after another. Ear, sinus, and other infections may not improve with treatment as expected, but keep coming back or occurring with less common but severe infections, such as recurrent pneumonia. Besides being painful, frightening, and frustrating, these constant infections can cause permanent damage to the ears or to the lungs.

In the more severe forms of PI, germs which cause only mild infections in people with healthy immune systems may cause severe or life-threatening infections.

Although infections are the hallmark of PIs, they are not always the only health problem, or even the main one. Some PIs are associated with other

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<sup>6</sup> This and other passages have been adapted from the NIH and NICHD:

<http://www.nichd.nih.gov/default.htm>. "Adapted" signifies that the text has been reproduced with attribution, with some or no editorial adjustments.

<sup>7</sup> Adapted from the National Institute of Child Health and Human Development (NICHD): <http://www.nichd.nih.gov/publications/pubs/primaryimmunobooklet.htm>.

immune system disorders, such as anemia, arthritis, or autoimmune diseases. Other PIs involve more than the immune system; some, for instance, are associated with symptoms involving the heart, digestive tract, or the nervous system. Some PIs retard growth and increase the risk of cancer.

Today, thanks to rapid advances in medicine, many PI diseases can be successfully treated or even cured. With proper treatment, most people with PIs are not only surviving once-deadly diseases, they are usually able to lead normal lives. Children usually can go to school, mix with playmates, and take part in sports. Most adults with PI are leading productive lives in their communities.

Successfully combating PI, however, depends on prompt detection. Physicians, parents, and adult patients alike need to recognize when infections are more than “ordinary,” so that treatment can be started in time to prevent permanent damage or life-threatening complications.

This booklet is designed to make PIs easier to recognize, and to cope with, by making them more familiar. It describes how these diseases arise, how they affect health, and how they can be treated. It also reports on promising areas of research, and suggests sources of help for patients and their families. It is not intended as a substitute for professional medical care. You should consult your pediatrician or family physician for specific information on the diagnosis, treatment, and clinical care of patients with PI.

A PI disease results whenever one or more essential parts of the immune system is missing or not working properly at birth because of a genetic defect. Since the immune system is tremendously complex, hundreds of things can go wrong during development and sometimes the backup systems cannot compensate for the defects. (See section on The Immune Defenses)

A variety of developmental errors in the immune system create different types of PIs. They make people susceptible to different kinds of germs and create different sets of symptoms.

PI diseases were once thought to be rare, mostly because only the more severe forms were recognized. Today physicians realize that PIs are not uncommon. They are sometimes relatively mild, and they can occur in teenagers and adults as often as in infants and children.

Very serious inherited immunodeficiencies become apparent almost as soon as a baby is born. Many more are discovered during the baby's first year of life. Others—usually the milder forms—may not show up until people reach their twenties and thirties. There are even some inherited immune deficiencies that never produce symptoms.

The exact number of persons with PI is not known. It is estimated that each year about 400 children are born in the United States with a serious PI. The number of Americans now living with a primary immunodeficiency is estimated to be between 25,000 and 50,000.

As new laboratory tests become more widely available, more cases of PIs are being recognized. At the same time, new types of PI are being discovered and described.

Currently, the World Health Organization lists over 70 PIs and the numbers are increasing. Among the rarest forms of immune deficiency is Severe Combined Immune Deficiency (SCID). SCID has been reported in small numbers, while some deficiencies, like DiGeorge Anomaly, are diagnosed more commonly.

At the other extreme, an immune disorder called Selective IgA Deficiency may occur in as many as one in every 300 persons. This figure is an estimate, based on studies of blood from blood donors, since most people with IgA deficiency are healthy and never realize they have this disorder.

## **Where Do Primary Immunodeficiency Diseases Come From?**

PI diseases are usually inherited. Like anything that is inherited, these diseases are the result of altered or mutated genes that can be passed on from parent to child or can arise as genes are being copied. One or both parents, usually healthy themselves, may carry a gene (or genes) that is somehow defective or mutated, so that it no longer produces the right protein product. If their child inherits a defective gene and does not have a normal gene to compensate, the child may show signs of immunodeficiency. The loss of just one small molecule, if it is an important one, can impair the body's immune system.

Sometimes close relatives—brothers, sisters, cousins—also inherit the defective gene. If they do not inherit a normal gene copy they may also have immunodeficiency. In some PIs, some relatives may have only mild symptoms, while others may have no symptoms at all. It is also possible to

develop, or acquire, an immunodeficiency disorder during one's lifetime. This can be the result of immune system damage due to an infection, as is the case with AIDS—the acquired immune deficiency syndrome. AIDS is caused by infection with HIV, the human immunodeficiency virus, which infects immune cells and destroys the immune system. When

HIV is transmitted from the mother to the baby, congenital AIDS may occur; but the disease is viral and not inherited. An immunodeficiency can also develop as the unintended side-effect of certain drug or radiation treatments, such as those given to cancer or transplant patients.

The focus of this booklet is primary immunodeficiency disease that is heritable. It is carried through the genes; you cannot “catch it” like a cold.

## **The Immune Defenses**

The immune defense system is a body-wide network of organs, tissues, cells, and protein substances that work together to defend the body against attacks by “foreign” invaders. Those invaders are primarily germs—tiny, infection-causing organisms such as bacteria and viruses, parasites and fungi. (See box on Germs)

The immune system is amazingly complex. It can recognize millions of different enemies, and it can enlist specialized cells and secretions to seek out and destroy each of them. (Substances recognized as foreign that provoke an immune response are called antigens.)

The organs of the immune system are known as lymphoid organs because they are home to lymphocytes, small white blood cells that are key components of the immune defenses. Bone marrow is soft tissue in the hollow center of bones, and it is the original source of all blood cells. The thymus is an organ that lies behind the breastbone; that is where some lymphocytes mature. The spleen, located in the upper left of the abdomen, serves as headquarters for many immune system activities.

Lymphocytes can travel throughout the body, using the blood vessels or a system of lymphatic vessels. The lymphatic vessels carry a clear fluid known as lymph. Scattered along the lymphatic vessels are small, bean-shaped lymph nodes, where immune cells gather and interact.



Clumps of lymphoid tissue are found in many parts of the body, especially in the linings of the digestive tract and the airways and lungs—areas that protect gateways into the body. These tissues include the tonsils, adenoids, and appendix.

The immune system makes use of many types of white blood cells. These include two main kinds of lymphocytes, T lymphocytes (T cells) and B lymphocytes (B cells); and a class of cytotoxic lymphocytes called natural killer (NK) cells. Additionally, there are large white blood cells known as phagocytes (neutrophil and monocyte).

## **Types of White Blood Cells**

Immune cells, once alerted to danger, undergo important changes. They begin to produce powerful chemicals that allow the cells to grow and multiply, and to attract and direct their fellow cells.

To work well, most immune cells need the help of other immune cells. Sometimes immune cells communicate with one another by direct physical contact, sometimes by releasing chemical messengers.

Each type of immune cell has its special role. B cells work chiefly by making plasma cells that secrete antibodies. Antibodies are large molecules that attach to invading germs (and other foreign particles) and mark them for destruction.

T cells contribute to the immune defenses in two major ways. Helper T cells and cytotoxic T cells secrete powerful chemicals (cytokines) that allow them to control the immune responses, including the work of B cells. Natural killer cells directly attack cells that have been infected by viruses.

Phagocytes are large white blood cells that act as scavengers. They roam through the body, engulfing germs and destroying them. Neutrophils and monocytes are phagocytes that contain bags of potent chemicals that help destroy the germs they engulf.

Antibodies are blood proteins known as immunoglobulins. They are produced by B cells. Different types, or classes, of immunoglobulins play different roles in immune defenses. As an immune response unfolds, B cells gradually switch from making one type of immunoglobulin to another.

- Immunoglobulin M (IgM) is the first to respond to an invading germ. IgM antibodies tend to stay in the bloodstream, where they aid in killing bacteria.
- Immunoglobulin G (IgG) follows on the heels of IgM. It is the main immunoglobulin working in the blood and tissues. IgG antibodies coat germs so that immune cells have an easier time of engulfing them.
- Immunoglobulin A (IgA) is produced along surface linings of the body and secreted in body fluids such as tears, saliva, and mucus, where it protects the entrances to the body – mouth, nose, lungs, and intestines. It is also present in breast milk and provides important protection against bacteria in the intestines of newborns.
- Immunoglobulin E (IgE) which is normally present only in trace amounts, is an important component of allergic reactions.

Another important component of the immune defenses is the complement system. The complement system is composed of a series of more than 20 blood proteins that, when activated, work closely together in a step-wise fashion. Complement helps antibodies and phagocytes destroy bacteria and acts as a signal for recruiting phagocytes to sites of infections.

Although the immune system is designed to recognize and attack foreign invaders, its recognition program sometimes breaks down. Then the body begins to make T cells and antibodies directed against its own cells and organs. These misguided T cells and these autoantibodies, as they are known, contribute to “autoimmune” diseases. For instance, T cells that attack pancreatic islet cells contribute to diabetes, while certain autoantibodies are common in persons with rheumatoid arthritis.

## Genes and PI

In the past few years, scientists have succeeded in identifying the genes that are responsible for many PI diseases. These include X-Linked Agammaglobulinemia, X-linked Hyper-IgM Syndrome, Wiskott-Aldrich Syndrome, Ataxia Telangiectasia, four forms of Chronic Granulomatous Disease, and several forms of SCID. The search for other genes that cause PI is under way and more are being discovered.

Sometimes the same, or nearly the same, symptoms can be the product of different defective genes on different chromosomes. For example, SCID can be caused by mutations in different genes. One genetic defect blocks

activation of B cells and T cells. Another genetic defect prevents immune cells from getting rid of toxic chemicals. In every case, however, the end result is the same: major immune defenses are non-functional.

Once researchers have identified the defective gene, they try to find out what it normally does, what protein it makes, and how that protein contributes to the immune response. Some proteins, for example, relay signals that tell immune cells to multiply and mature. Other proteins help the immune system to eliminate excess or unwanted cells.

The next step is to ascertain what happens when the protein is missing or distorted and how the faulty protein causes disease.

Learning about a disease-causing gene and its protein product raises the exciting prospect of finding a cure for the disease.

One possibility might be to replace a mutated gene through gene therapy. Another way might be to supply the missing protein as a medicine.

## **Germ**s

Germ

s include the following types of organisms:

- Bacteria
- Viruses
- Parasites
- Mycoplasma
- Fungi

### **Bacteria**

Bacteria are tiny living organisms. Each bacterium consists of a single cell, but bacteria often live in colonies. Most are harmless or even beneficial, but some can cause illness and death.

Bacteria are responsible for many respiratory, skin, and bone infections. Examples of infection-causing bacteria include “strep” (Streptococcus) and “staph” (Staphylococcus).

## **Viruses**

Viruses consist of the barest essentials: a strand of genetic material, either DNA or RNA, surrounded by a protein coat. Some viruses also have an outer envelope. Viruses are so simple that, in order to reproduce, they need to invade a living cell and use the cell's machinery.

Different types of viruses target different types of cells. Some viruses kill the cell they invade. Others permanently change the way the cell behaves.

Viruses cause the flu (or influenza, a highly contagious respiratory infection), colds, polio, hepatitis (liver inflammation), and measles. A single virus family, Herpes viruses, causes everything from cold sores to chicken pox.

## **Parasites**

Parasites live, grow, and feed on other organisms, which serve as their "hosts." Parasites come in many shapes and sizes, and they cause a wide range of diseases.

Microscopic one-cell parasites known as *Cryptosporidium* and *Giardia lamblia* cause diarrhea and inflammation of the digestive system. *Pneumocystis carinii* can cause pneumonia, and *Toxoplasma gondii* can produce brain inflammation.

## **Mycoplasma**

Mycoplasma are simpler than bacteria but more complex than viruses. They are the smallest known organisms that can live without a host. Mycoplasma can cause pneumonia and a type of arthritis.

## **Fungi**

Fungi, which are primitive plant forms, include yeasts and molds. As a cause of disease, they are especially dangerous for persons with impaired immunity.

A fungus called *Candida albicans* causes thrush, which commonly forms a white mat coating on the inside of the mouth in severely immunodeficient people. This fungus may also cause esophagitis, a type of diaper rash, or a

blood infection. *Cryptococcus* can cause meningitis, an inflammation of the membranes surrounding the brain and spinal cord. *Aspergillus*, an ordinarily harmless mold, can cause severe infections in those with PI, especially infections of the lung.

## Signs and Symptoms

The most common problem in PI disease is an increased susceptibility to infection. For people with PI, infections may be common, severe, lasting, or hard to cure.

Even healthy youngsters may get frequent colds, coughs, and earaches. For example, many infants and young children with normal immunity have one to three ear infections per year. Children with PI, however, can get one infection after another. Or they get two or three infections at a time. Weakened by infection, the child may fail to gain weight or fall behind in growth and development.

Despite the usual antibiotics, the infections of PI often drag on and on, or they keep coming back—that is, they become chronic. One common problem is chronic sinusitis (infection and inflammation of the sinuses, air passages in bones of the cheeks, forehead, and jaw). Another common problem is chronic bronchitis (infection and inflammation of the airways leading to the lungs).

Serious infections, especially bacterial infections, may cause a youngster to be hospitalized repeatedly. Pneumonia is an infection of the smallest airways and airsacs in the lungs, which prevents oxygen from reaching the blood and makes breathing hard. Meningitis, an infection of the membranes that surround the brain and spinal cord, causes fever and severe headache, and can lead to seizures, coma, and even death. Osteomyelitis is an infection that invades and destroys bones. Cellulitis is a serious infection of connective tissues just beneath the skin.

Some people with PI develop blood poisoning, an infection that flourishes in the bloodstream and spreads rapidly through the body. Some people may develop deep abscesses, pockets of pus that form around infections in the skin or in body organs.

Some children with PI are infected with germs that a healthy immune system would hold in check. These are known as “opportunistic” infections because

the germs take advantage of the opportunity afforded by a weakened immune system. Such an unusual infection may be the tip-off to an immunodeficiency.

For example, *Pneumocystis carinii* is a microscopic parasite that infects many healthy people without making them sick. But when the immune system is compromised, *Pneumocystis* can produce a severe form of pneumonia.

*Toxoplasma* is another widespread parasite that usually produces no disease. In persons with a weakened immune system, it causes toxoplasmosis, which can be a life-threatening infection of the brain that can cause confusion, headaches, fever, paralysis, seizures, and coma.

Besides all the infections, some immunodeficiency diseases produce other immune system problems, including autoimmune disorders. Autoimmune disorders develop when the immune system gets out of control and mistakenly attacks the body's own organs and tissues.

In some autoimmune disorders, the faulty immune system targets a single type of cell or tissue. For example, an immune attack on blood cells can lead to anemia (a debilitating loss of red blood cells). An attack on islet cells of the pancreas can lead to diabetes (a disorder caused by insufficient amounts of insulin, a pancreatic hormone that helps the body convert digested food into energy).

In other situations, the immune system strikes multiple cells and tissues, producing diseases such as rheumatoid arthritis or systemic lupus erythematosus (SLE). Rheumatoid arthritis targets primarily the joints, but it can also damage nerves, lungs, and skin. Lupus strikes skin, muscles, joints, kidneys, and other organs, causing rashes, joint pain, fatigue, and fever, among other things.

Finally, an immunodeficiency can be just one part of a complex syndrome, with a telltale combination of signs and symptoms. For example, children with DiGeorge Anomaly not only have an underdeveloped thymus gland (and a corresponding lack of T cells), they typically have congenital heart disease, malfunctioning, or underdeveloped parathyroid glands, and characteristic facial features. Young boys with Wiskott-Aldrich Syndrome, in addition to being prone to infections, develop bleeding problems and a skin rash.

## The 10 Warning Signs of Primary Immunodeficiency<sup>8</sup>

- Eight or more new ear infections within a year.
- Two or more serious sinus infections within a year.
- Two or more months on antibiotics with little effect.
- Two or more pneumonias within a year.
- Failure of an infant to gain weight or grow normally.
- Recurrent deep abscesses in the skin or organs.
- Persistent thrush in mouth or on skin, after age one.
- Need for intravenous antibiotics to clear infections.
- Two or more deep-seated infections such as meningitis, osteomyelitis, cellulitis, or sepsis.
- A family history of primary immunodeficiency.

## DNA, Genes, and Chromosomes

All our traits—height, eye color, foot size—are determined by the genes that we inherit from our parents. A gene is a working subunit of DNA. DNA is like a huge database, made up of millions of chemical building blocks. DNA resides in the core of every cell, and it carries a complete set of instructions, or blueprint, for making everything the cell will ever need.

The DNA in each human cell contains about 100,000 genes. Each gene encodes the instructions that allow the cell to make one specific product—for example, a protein such as an enzyme. (Proteins are major components of all cells. Enzymes are proteins which help carry out chemical reactions.)

When genes are working properly, our bodies develop correctly and work well. But small changes, or mutations, in just one gene sometimes can have huge effects, leading to birth defects and other diseases.

DNA is packaged in structures known as chromosomes. Chromosomes come in pairs, and a normal human cell contains 46 chromosomes. These consist of 22 pairs of “autosomes” and two “sex chromosomes,” X and Y. A female has two X chromosomes while a male has one X and one Y.

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<sup>8</sup> Courtesy of the Jeffrey Modell Foundation and the American Red Cross.

We inherit one chromosome of each pair from our mother and the other from our father. Since genes are lined up on the chromosomes, we thus inherit two copies of most genes, one from each of our parents.

If one copy of a gene is not working properly, its partner from the other parent can often compensate. However, this is not possible if both copies of the gene are defective or, in the case of an X chromosome gene defect in a boy, where there is only one X chromosome.

## **Patterns of Inheritance**

Scientists studying inherited diseases group them according to the way in which the disease-causing gene is passed on. In general, “recessive” diseases occur when there is no normal copy of a gene to compensate for a defective one, while “dominant” diseases are manifest even with one normal and one abnormal gene copy. Diseases caused by defects in a single gene fall into one of the following categories:

### **X-Linked Recessive Diseases**

X-linked recessive diseases are caused by genes located on the X chromosome. Although we have two copies of most genes, men have only one X chromosome and only one copy of genes on that X chromosome. If a man inherits a disease-causing gene mutation that is on the X chromosome, he has no backup normal X gene, and he will likely develop the disease.

A woman will not usually develop an X-linked recessive disease because she has two X chromosomes, but she can be a “carrier.” She remains healthy because the normal gene on one X chromosome continues to function, even though she carries the mutated gene, and can pass it on to her children. With each and every pregnancy, there is an equal chance that the baby will be a boy with the disease, a healthy girl who is a carrier, a healthy boy, or a healthy girl who is not a carrier.

For some X-linked recessive immunodeficiency diseases, carriers can be identified by laboratory tests. With others, a woman is discovered to be a carrier only after she gives birth to a child with the disease.



### **Autosomal Recessive Diseases**

Autosomal recessive diseases occur when a person inherits two faulty recessive genes located on autosomes (non-sex chromosomes), one from each parent; both parents are healthy carriers. These diseases are as likely to affect girls as boys. With every pregnancy, there is one chance in four that the baby will have the disease, two chances in four that the baby will be healthy but a carrier, and one chance in four that the child will be healthy and not carry a defective copy of the gene.

### **Autosomal Dominant Disorders**

Autosomal dominant disorders are caused by a single dominant gene. One of the parents is not just a carrier, but has the disease. Each child in the family has a 50-50 chance of inheriting the defective gene and the disorder.

### **New Mutations**

New mutations may cause diseases. In some cases, neither parent has the disease-causing mutation. This may occur because the mutation in the gene occurred in the parents' germ cells (sperm or egg) but not other cells of their body. New mutations account for a substantial proportion (up to one-third) of X-linked immunodeficiency diseases.

Although many PI diseases can be traced to a single gene, others cannot. No family pattern is evident, and they are said to occur "sporadically."

### **Sporadic Disorders**

A sporadic disorder might be the result of several disabled genes interacting, interactions between particular forms of genes, and environmental influences. It might develop from gene changes that occur during a person's lifetime. Or it might be due to new mutations in germ cells or an inheritance pattern that has not been recognized yet.

Some PIs are X-linked, others autosomal recessive. At least one is autosomal dominant. Some PIs have more than one pattern of inheritance. For example, a group of diseases known as Common Variable Immunodeficiency (CVID) can be inherited as autosomal recessive, autosomal dominant, or X-linked. Most cases of CVID, however, are sporadic.

## Diagnosing PI

Sometimes the signs and symptoms of a PI are so severe, or so characteristic, that the diagnosis is obvious. In most cases, it is not clear if a long string of illnesses are just “ordinary” infections, or if they are the result of an immunodeficiency.

Many conditions can produce an immunodeficiency, at least temporarily, and most children who seem to have “too many” infections are not, in fact, suffering from an immunodeficiency. Experts estimate that half of the children who see a doctor for frequent infections are normal. Another 30 percent may have allergies, and 10 percent have some other type of serious disorder. Just 10 percent turn out to have a primary or secondary immunodeficiency.

### The Basics

When a pattern of frequent infections suggests an immunodeficiency, the doctor begins by exploring the patient’s “history” and the family’s history, and then conducts a physical examination.

The patient’s history:

- What infections has the patient had in the past, or has now?
- Have they been unusually frequent, or severe, or long-lasting?
- Have they failed to respond to standard treatments?
- When a child who is immunologically normal develops a string of infections, they are usually mild and short-lived, and between infections the child recovers completely.
- What, besides a PI, might explain the high rate of infections?

Normal immune responses can be suppressed by many factors, including malnutrition, injuries such as burns, and certain types of drugs (corticosteroids, for instance). Immune responses can also be muted by some diseases, such as leukemia, and some infections, including: infectious mononucleosis (mono), measles, chicken pox, and AIDS. In fact, almost every serious illness impairs the immune responses.

Physical examination:

- Is the child well-nourished and growing well? A severely immunodeficient child is likely to look sickly and pale. Very often the child is underweight and lags behind in growth and development.
- The child may be shy or quiet. An active, robust, healthy-looking child is less likely to have a serious immune deficiency.
- The doctor will listen for changes in the lungs and look for rashes, sores, thrush in the mouth, an enlarged spleen or liver, and swollen joints. Some immunodeficient children may lack palpable tonsils or lymph nodes in the neck.

Family history:

- Have any family members or relatives ever been diagnosed with PI or shown an unusual susceptibility to infections?
- Have there been any infant deaths from infections?
- Were only boys affected?

### **Evaluating Immune Responses**

To find out if illness can be traced to an immunodeficiency, laboratory tests are necessary. These tests, most of which can be performed on a sample of blood, probe the soundness of the various parts of the immune system. Are all the right immune cells present, in adequate numbers, and are they working properly? Are there normal amounts and types of antibodies?

Screening starts out with a few relatively simple and inexpensive routine tests. In fact, just two routine tests—complete blood count and quantitative immunoglobulins—will detect most, but not all, immunodeficiencies.

If antibodies are normal—or if the patient's infections seem to be caused by viruses or fungi—the T cells should be checked. If the T cells are present in normal numbers and function normally, phagocyte function should be evaluated.

The most common screening tests include:

- Blood count. A complete blood count (CBC) shows levels of red blood cells and white blood cells as well as platelets. A “differential count” itemizes the different types of white blood cells, including lymphocytes and neutrophils.

- **Quantitative immunoglobulins.** This standard laboratory test measures various immunoglobulin levels in the blood. In addition to total immunoglobulins, it shows levels of the different immunoglobulin types (IgG, IgM, and IgA).
- **Antibody responses.** Are immunoglobulins working properly? A blood test can show if the blood contains antibodies to the usual childhood immunizations, i.e., tetanus, measles, pertussis, or diphtheria. Sometimes a person may be given a booster shot, or a specific immunization such as a tetanus shot, to see if she or he responds by producing antibodies.
- **Complement.** A laboratory test using a sample of blood indicates how effectively the complement system is working.
- **Skin tests.** These tests, which are similar to TB skin tests, show how well T cells are functioning. Tiny amounts of several standard reaction-provoking antigens (including mumps and Candida) are injected into the skin. A person with a healthy immune system usually develops local swelling within 24 to 48 hours. However, these tests are not as accurate in very young infants.

When screening tests indicate an immunodeficiency—or when they fail to explain a stubborn infection—additional tests will likely be needed. There are dozens of sophisticated tests that allow doctors to identify and count subsets of B cells and T cells, and to assess subtle abnormalities in antibodies, immune cells, and immune tissues. Tests can also probe the characteristics of infectious germs.

### **Evaluating Infections**

If an infection proves resistant to standard treatments, the doctor will want to find out exactly what germs are involved. Samples of mucus, sputum, or stool, or sometimes a small sample of the infected tissue itself, removed surgically, can be “cultured” in the laboratory. This allows germs to grow until they are plentiful enough to study in detail. Once the germ is identified, it becomes possible to select the most effective treatment.

The infection itself often provides a good clue to the nature of an immune defect. Common bacteria typically elicit antibodies, while viruses and fungi stimulate T cells. Thus, sinus infections and respiratory infections, which are most often due to bacteria, suggest an antibody deficiency. Infections caused by a variety of viruses and fungi, or by *Pneumocystis*, point to a T cell defect. Recurrent infections involving the skin or soft tissues can often be traced to

problems with phagocytes. Blood-borne infections caused by encapsulated bacteria, including meningitis, may be linked to complement deficiencies.

An experienced physician will also find clues in particular combinations of details, such as age and sex, along with the physical findings. For example, a young infant suffering from diarrhea, pneumonia, and thrush, and exhibiting “failure to thrive,” may well have SCID. A 4-year-old with swollen lymph glands, skin problems, pneumonia, and bone infections may have Chronic Granulomatous Disease (CGD). A 10-year old with sinus and respiratory infections, an enlarged spleen, and signs of autoimmune problems is apt to have Common Variable Immunodeficiency.

### **Prenatal Diagnosis**

Some PIs can be detected even before birth. Prenatal testing may be sought by families that have already had a child with a PI.

Cells for prenatal diagnosis can be obtained in several ways. In amniocentesis at about 14 weeks of pregnancy or later, a small amount of amniotic fluid containing cells shed by the fetus is removed from the uterus. In chorionic villus sampling, cells are taken from the chorion, the tissue that becomes the placenta, as early as 9–10 weeks of pregnancy. After about the 18th week of pregnancy, it is possible to obtain a sample of blood from the fetus.

Prenatal tests make it possible to identify abnormalities in cells or, in the case of some deficiencies, of enzymes. In disorders where a gene mutation has been identified, DNA from fetal cells can be checked for the gene defect.

In some cases, test results make it possible to be ready to treat the baby with a bone marrow transplant soon after birth. Intrauterine bone marrow transplantation of the fetus is also being studied.

### **Treatments for PI**

Treating PI involves not only curing infections but also correcting the underlying immunodeficiency. In addition, any associated conditions, such as autoimmune disorders or cancer, need special attention.

## **Treating Infections**

The first goal of treatment is to clear up any current infection. Doctors can prescribe a wide range of infection-fighting antimicrobials. Some are broad-spectrum antibiotics that combat a range of germs. Others zero in on specific germs.

When an infection fails to respond to standard medications, the patient may need to be hospitalized to be treated with antibiotics and other drugs intravenously.

For chronic infections, a variety of medicines can help relieve symptoms and prevent complications. These may include drugs like aspirin or ibuprofen to ease fever and general body aches, decongestants to shrink swollen membranes in the nose, sinuses, or throat, and expectorants to thin mucus secretions in the airways.

People who have chronic respiratory infections may be made more comfortable with a technique known as postural drainage (or bronchial drainage). Developed for persons with cystic fibrosis, postural drainage uses gravity, along with light blows to the chest wall, to help clear secretions from the lungs.

## **Bone Marrow Transplantation (BMT)**

In bone marrow transplantation (BMT), bone marrow is taken from a healthy person and transferred to the patient. Because bone marrow is the source of all blood cells, including infection-fighting white blood cells, a successful bone marrow transplant amounts to getting a new, working immune system.

BMT usually takes place in the hospital. The donor is put to sleep with a light general anesthesia, and bone marrow is removed through a large needle inserted into the pelvic bone in the lower back. A small amount of marrow is removed from each of several sites.

The bone marrow may be treated to remove mature T cells which could attack the recipient's tissues. It is then given to the patient like an ordinary blood transfusion. Marrow cells travel to the patient's own marrow spaces, inside the bones. There they begin making a complete assortment of healthy blood cells.

## Preventing Infections

When the immune defenses are weak, it is essential to avoid germs. Precautions range from common sense practices like good hygiene (using mild soaps to keep the skin clean and brushing teeth twice a day) and good nutrition to elaborate measures to prevent all contact with infectious agents.

Anyone with an immunodeficiency needs to avoid unnecessary exposure to infectious agents. This means staying away from people with colds or other infections, and avoiding large crowds. (On the other hand, it is important not to become overly cautious. Children are encouraged to attend school, to play in small groups, and to participate in sports.)

Antibiotics are important for preventing or controlling infections. If infections threaten to become chronic, the doctor may prescribe continuous long-term low-dose antibiotics. Such preventive, or “prophylactic,” therapy may help prevent hearing loss or permanent breathing problems.

When *Pneumocystis pneumonia* is a danger—for instance, in children with a profound T cell deficiency—an appropriate prophylactic treatment may consist of a combination of two drugs, trimethoprim and sulfamethoxazole.

## Correcting Immunodeficiencies

Not long ago, little could be done to actually cure an immunodeficiency. Today, researchers have developed several possibilities for replenishing the immune defenses. No single approach works for all immunodeficiencies or in all cases but, taken together, these new treatments have transformed a dismal prognosis into one of hope and promise.

For several life-threatening immunodeficiencies, bone marrow transplantation (BMT) offers the chance of a dramatic, complete, and permanent cure. Since the first BMT was performed in 1968, nearly 1,000 children with PI, including SCID, Wiskott-Aldrich Syndrome, Leukocyte Adhesion Defect, and other disorders, have shown a remarkable recovery. They recover from infections, gain weight, and move on to essentially normal lives.

Unfortunately, bone marrow transplants don’t work for everyone. To be successful, the transplant needs to come from a donor whose body tissues are a close biological “match.” That is, the donor’s tissues and the recipient’s

tissues should have identical, or nearly identical, sets of marker molecules (known as HLA antigens) that serve as unique tissue ID tags.

Without a good match, a reaction known as graft-versus-host disease (GVHD) may occur, in which cells in the donor marrow see the recipient's tissues as foreign and react against them.

Because tissue marker molecules come in many varieties, finding a good match is not easy. With new techniques and the availability of large donor banks, however, finding a suitable match is easier. The best matches are likely to be with close relatives, especially brothers or sisters.

Another option is marrow from a close relative—typically a parent—who shares half of the patient's major HLA antigens (and many of the minor antigens as well.) Cleansed of mature T cells that could trigger a GVHD, such half-matched transplants have saved the lives of many children.

BMT works especially well for SCID, because children with SCID lack T cells that could attack the bone marrow graft and cause rejection. Anyone with T cells may need to be treated, prior to transplantation, with radiation or drugs. Although this eliminates the recipient's T cells, it also temporarily wipes out other immune defenses, further increasing the patient's risk of infection.

Even with a good match, BMT does not always succeed. Results are best when the child is young, in fairly good health, and free of serious infection at the time of the transplantation.

Another treatment option, for children with a specific form of SCID who don't have a suitable bone marrow donor, is enzyme replacement therapy. About 15 percent of all cases of SCID are due to lack of the enzyme known as adenosine deaminase (ADA). This type of SCID can be partially treated with regular injections of the missing enzyme. For treatment, ADA is linked to a chemical, polyethylene glycol (PEG), which protects ADA from being quickly eliminated from the bloodstream.

For many people with antibody deficiencies, antibody replacement therapy can be a lifesaver. The patient receives regular infusions or injections of immunoglobulins, or antibodies, that have been removed from the blood of healthy donors and purified. Immunoglobulins from thousands of donors are pooled so that each batch contains antibodies to many different types of germs. Because purification removes most IgM and IgA, the product consists



almost entirely of IgG. It is known as gammaglobulin, immunoglobulin, or immune serum globulin.

Taken regularly and in large doses, gammaglobulins can boost serum immunoglobulins to near normal levels and eliminate most infections. If treatment begins early enough, it can prevent lung damage from pneumonia.

Immunoglobulin is administered either intramuscularly or intravenously. Intravenous immunoglobulin (IVIG) is usually preferred because it can be given in large doses, it is fast-acting, and it avoids the pain associated with large intramuscular injections. Infusions of IVIG take two to four hours and are administered every three or four weeks, either at home or in an outpatient clinic.

Injections of cytokines, which are natural chemicals produced by immune cells, are another new way to treat immune deficiencies. For example, the symptoms of Chronic Granulomatous Disease can be traced to faulty phagocytes; phagocytes can be activated with injections of a natural or synthetic product of immune cells called gamma interferon.

In some immune deficiencies, the numbers of neutrophils may be reduced either because they are under attack or are not produced in normal numbers. In certain cases, this problem can be offset by the injection of growth factors. These growth factors increase the production of neutrophils. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a natural chemical that boosts the development of blood cells, including the white blood cells known as granulocytes and macrophages. Another granulocyte colony-stimulating factor (G-CSF), is also helpful in raising levels of granulocytes.

### **Transplanting Cells from Umbilical Cord Blood**

Transplanting cord blood stem cells is even newer than transplanting bone marrow, and easier. Stem cells are long-lived parent cells that continually give rise to fresh blood cells. Ordinarily, they live in the bone marrow. Some stem cells circulate in the blood, but they are scarce and difficult to extract. However, stem cells are plentiful in blood in the umbilical cord of healthy infants at the time of birth.

To obtain cord blood stem cells, blood is drained from the umbilical cord and placenta as soon as a healthy baby is born and the cord clamped and cut. The cord blood is typed, frozen and stored. Later it can be transplanted into a matched recipient with an immunodeficiency.

Doctors have used stem cells from cord blood to treat a variety of blood diseases in children. The cord blood has usually come from cord blood banks.

Research suggests that cord blood stem cells may not need to be matched as closely as bone marrow.

## **Important Precautions**

Children with PI diseases, especially those with defective T cells, X-linked agammaglobulinemia, and ataxia telangiectasia should not receive live virus vaccines, such as the oral polio, measles, and chicken pox (varicella) vaccines. It is not even safe to give live virus vaccines to children suspected of immunodeficiency until a definitive diagnosis is rendered. There is a risk that such vaccines could cause serious illness or even death. Moreover, blood transfusions should not only be free of infectious viruses (e.g., hepatitis or cytomegalovirus), but also—for T cell deficient children—irradiated to incapacitate mature donor T cells that might attack the tissues of the recipient and result in GVHD.

## **Primary Immunodeficiency Diseases: Some Examples**

Primary immunodeficiencies are complex diseases. Since each one can be traced to the failure of one or more parts of the immune system, one of the more convenient ways to group them is according to the part of the immune system that is faulty:

- B cell (antibody) deficiencies
- Combined T cell and B cell (antibody) deficiencies
- T cell deficiencies
- Defective phagocytes
- Complement deficiencies
- Deficiencies/cause unknown

## **B Cell (Antibody) Deficiencies**

More than half of all PIs are caused by a lack of infection-fighting antibodies (immunoglobulins). The person has either too few antibody-producing B cells or B cells that don't work properly.

In some disorders, the B cells make almost no antibodies, leaving the person susceptible to a wide range of infections. In others, the B cells make some antibodies, but not enough to give strong protection. In yet other conditions, the B cells fail to make special subsets of antibodies, creating a risk for just certain kinds of infections.

### **X-Linked Agammaglobulinemia (XLA)**

X-Linked Agammaglobulinemia (XLA) youngsters make no antibodies at all (a = without, gammaglobulin = antibodies, emia = in the bloodstream). These patients have few or no mature B cells or antibody-secreting plasma cells.

It is called X-linked because the mutated gene responsible for the disease is located on the X chromosome. (This gene encodes an enzyme necessary for B cell development.) As an X-linked disease, XLA affects only males. (See section on Genetics)

For their first few months, baby boys who have inherited XLA are healthy, protected by IgG they received from their mothers via the placenta before birth and in the breast milk after birth. As the mother's IgG fades, however, the baby develops a steady stream of infections.

They get infections caused by bacteria that would normally be controlled by antibodies—ear infections, sinus infections, eye infections, skin infections, and pneumonia. They can also develop encephalitis, meningitis, or blood poisoning. Antibiotics clear up one infection, only to have another start up soon.

Boys with XLA are also susceptible to viruses that are normally neutralized by antibodies during their spread in the bloodstream. These include common viruses that cause diarrhea as well as viruses that cause liver disease (hepatitis) and polio. (An XLA child who receives oral polio vaccine risks paralysis.)

Laboratory tests show extremely low levels of B cells, especially the mature B cells capable of secreting immunoglobulins. Overall immunoglobulin levels in the blood are low, and specific antibodies—for instance, to any vaccines the child has received—are missing. Tissues rich in B cells such as tonsils and lymph nodes may be undersized or scanty.

Although XLA cannot be cured, it can be controlled with immunoglobulin therapy. Large doses of immune globulins, taken regularly for life, will prevent most infections. For the most part, these children will be able to live relatively normal and active lives.

### **Common Variable Immunodeficiency (CVID)**

Common Variable Immunodeficiency (CVID) is the name given to a group of disorders characterized by low levels of gammaglobulins and too few IgA antibodies. People with CVID may have normal numbers of B cells, but their B cells don't function properly. Their T cells also show a variety of defects.

This disease—also known as hypogammaglobulinemia (hypo = low, gammaglobulin = antibodies, emia = in the blood)—can occur in children, but it is more common in people in their twenties or thirties. It affects both men and women. Most patients have no family history of CVID, but they may have relatives with Selective IgA Deficiency.

Like most antibody deficiencies, CVID causes frequent bacterial infections, typically involving the ears, sinuses, and airways. Many CVID patients experience several bouts of pneumonia and some develop infections in joints, bones, and skin.

About a quarter of the people with CVID develop immune system illnesses, including anemia and rheumatoid arthritis. They also have an increased risk of cancer.

Disorders of the digestive tract are common. In addition to diarrhea caused by *Giardia* parasites, people with CVID are prone to inflammatory bowel diseases such as ulcerative colitis, or even colon cancer. Many have an enlarged spleen and swollen lymph glands, and some develop lymph system cancer (lymphoma).

Tests helpful in diagnosing CVID include measures of IgG and IgA levels in the blood and measures of antibody responses to immunizations.

Although antibiotics will help to control infections, the cornerstone of treatment is gammaglobulin therapy. Gammaglobulins will raise antibody levels and fend off infections, allowing many persons with CVID to enjoy a normal lifestyle.

### **Hyper-IgM Syndrome**

Hyper-IgM Syndrome youngsters often have high levels of IgM, the early-response antibody. However, they have no IgA, the class of antibody found in body fluids such as saliva, mucus, and tears, and they have very low levels of IgG, the common immunoglobulin in the blood. They also may have very low levels of the infection-fighting white blood cells called neutrophils.

The underlying problem in one form of Hyper-IgM involves T cells. In the X-linked form of Hyper-IgM Syndrome, the faulty gene fails to encode a molecule that normally permits T cells to communicate with B cells. B cells making IgM fail to get a signal from T cells, telling them to switch to making IgA and IgG.

Sometime before their first birthday, children with Hyper-IgM Syndrome begin to contract bacterial infections—ear infections, sinus infections, pneumonia, and tonsillitis. Many develop sores inside their mouths. In addition, they are susceptible to opportunistic infections, especially *Pneumocystis pneumonia*.

Another aspect of Hyper-IgM Syndrome is autoimmune disease. Autoimmune attacks on red blood cells lead to anemia, while autoimmune destruction of infection-fighting neutrophils further increases the risk of infection.

Many youngsters with Hyper-IgM Syndrome respond well to treatment, become symptom-free and resume normal growth. The cornerstone of treatment is regular IVIG, which not only supplies missing IgG antibodies, but also prompts a drop in IgM antibodies.

### **Selective IgA Deficiency**

Selective IgA Deficiency is characterized by a deficiency of immunoglobulins in body secretions and the mucous membranes lining the airways and

digestive tract. IgA normally stands guard at the body entrances, intercepting bacteria, viruses, toxins, and certain food components.

IgA Deficiency is the most common of the PIs. Studies of blood samples from blood bank donors show that IgA Deficiency occurs in as many as 1 of every 333 Americans with a Caucasian background.

Although this makes IgA Deficiency more common than all other immunodeficiencies combined, most people never know they have it. They remain healthy, with no more than the usual number of infections. Others suffer through more than their share of infections without ever knowing why.

When IgA Deficiency is diagnosed, it is usually because of an increase in the number of ear, sinus, and lung infections that are slow to respond to standard antibiotics. Treatment consists mainly of antibiotics, for specific infections and to prevent infections from becoming chronic.

IVIG isn't effective because there is no way to deliver IgA to mucous membranes. Moreover, some people with IgA Deficiency have anti-IgA antibodies, which can trigger a severe reaction to any blood products, including IVIG, that contain IgA.

The cause of IgA Deficiency is not known, and it may differ from one person to the next. B cells appear normal, but they seem unable to mature into cells capable of secreting IgA antibodies. Although no T cell defect has been found, some researchers suspect a problem with T cell regulation.

IgA Deficiency sometimes seems to run in families. It is more common among the relatives of people with CVID. In some cases, IgA Deficiency may progress to CVID.

IgA Deficiency itself seldom causes serious trouble. However, people with IgA Deficiency are very likely to have any of a variety of other problems. They are especially prone to allergies, including asthma; autoimmune diseases, including rheumatoid arthritis and diabetes; diseases of the gastrointestinal tract, and neurologic diseases. Thus anyone diagnosed with IgA Deficiency should have periodic checkups to look for such possibilities.

## **IgG Subclass Deficiency**

IgG Subclass Deficiency is another PI caused by the lack of certain antibodies. In this case, the person is missing one or two of the four subclasses of IgG (IgG1, IgG2, IgG3, and IgG4).

Each IgG subclass plays a slightly different role. IgG1 and IgG3 antibodies are formed in response to certain proteins, including toxins produced by some bacteria and the proteins of some viruses. IgG2 antibodies target the capsules that shield certain bacteria. Antibodies of some IgG subclasses cooperate with the complement system; others do not. As a result of such differences, each type of subclass deficiency leaves a person vulnerable to specific types of infections.

Overall IgG levels may be near normal, so it is necessary to measure each of the IgG subclasses. Patients may be immunized with a vaccine against encapsulated bacteria (such as *Streptococcus pneumoniae* or *Haemophilus influenzae*) to see if they respond with the appropriate antibodies.

Patients with IgG Subclass Deficiency have infections that are not as severe as those seen with broader immunoglobulin deficiencies such as XLA or CVID.

The usual treatment in IgG Subclass Deficiency consists of antibiotics to control and prevent infections. IVIG is usually reserved for children who are seriously ill and who are not responding to antibiotic therapy.

## **Combined T Cell and B Cell (Antibody) Deficiencies**

Some cases of PI are the result of a combined deficiency. Both of the immune system's major weapons—antibodies and T cells—are disabled. In some, the deficiency is almost total, and nearly any infection is a threat to life. In many combined immunodeficiencies, the pattern of signs and symptoms creates a distinctive syndrome.

## **Severe Combined Immunodeficiency (SCID)**

Severe Combined Immunodeficiency (SCID) is what most people think of when they hear about PI disease. It is the disease of “the boy in the bubble,” who spent his life in an isolation chamber to protect himself from germs.

SCID is rare; chances of a child being born with SCID are about one in 500,000 births. Until recent years, it was always fatal.

There are several major causes of SCID. Each is caused by a different genetic defect, and each develops along a different pathway. In X-linked SCID, the most common type, a genetic flaw damages molecules that allow T cells and B cells to receive signals from crucial growth factors. Another type of SCID is ADA Deficiency. This condition results from the lack of an enzyme that helps cells—especially immune cells—get rid of toxic byproducts. Without ADA, poisons build up and kill the lymphocytes. Purine nucleoside phosphorylase (PNP) Deficiency results from a similar enzyme problem, but B cells are less affected and the immunodeficiency is less severe, although affected patients may have other problems (neurologic).

Yet another variation is known as MHC Class II Deficiency or Bare Lymphocyte Syndrome. MHC molecules are specialized proteins found on the surface of body cells and play an important role in bone marrow transplantation. Class II MHC molecules, which appear on many immune cells, allow B cells and other immune cells to recognize, interact with, and activate T cells. Without this B cell/T cell communication, the immune defenses are compromised.

Whatever the underlying problem that causes SCID, the consequences are nearly always the same. The child lacks almost all immune defenses, develops life-threatening infections, and needs major treatment to survive beyond infancy. Although the specifics vary from case to case, these children are vulnerable to serious infections caused by bacteria, as is typical with a B cell deficiency, and also by viruses and opportunistic germs, as is the case with a T cell deficiency.

Usually by the time a baby is three months old, he or she (because many cases of SCID are X-linked, SCID is more common in boys than in girls) is likely to have persistent thrush or extensive diaper rash. Weakened by chronic diarrhea, the baby may stop growing and gaining weight. Some children develop a sharp, persistent cough with *Pneumocystis pneumonia*, blood disorders, or chronic hepatitis. Meningitis and blood poisoning pose a constant threat.

Viruses that are not harmful in children with normal immunity can pose a serious danger. For example, the virus that causes chicken pox (varicella) can trigger a severe infection in the lungs and the brain of SCID patients. Other threats come from the viruses that cause cold sores (herpes simplex) and measles (rubeola).



Laboratory tests confirm multiple problems. There may be extremely low levels of lymphocytes. B cells may be normal in number, but they don't function normally; immunoglobulin levels are low. There are few T cells, and those few are unresponsive. A chest x-ray may show that the thymus gland has failed to develop.

A diagnosis of SCID constitutes a medical emergency. The immediate concern is to bring any current infections under control, and to strengthen the baby's weakened condition with adequate nutrition. IVIG may help to bolster the immune responses.

A lasting remedy, however, requires a more drastic approach. A bone marrow transplant from a matched donor or parent is arranged as quickly as possible.

Children whose SCID is due to ADA Deficiency have another alternative. Injections of PEG-ADA will protect them against recurrent infections, allow them to control ordinary childhood infections such as chicken pox, and make it feasible for them to lead nearly normal lives.

## **Partial Combined Immunodeficiencies**

Partial Combined Immunodeficiencies are characterized by both the antibody and cell-based defenses being impaired, but not totally shut down. Problems are limited to certain functions of B cells and certain T cells. In these conditions, the immunodeficiency is part of a complex clinical picture. Other body systems are involved, too. The result is a distinctive set of symptoms, or a syndrome.

### **Wiskott-Aldrich Syndrome (WAS)**

Wiskott-Aldrich Syndrome (WAS) is characterized by a tendency to bleed easily and development of an intensely itchy, scaling skin rash (eczema). This is in addition to the severe recurrent infections seen in young boys who develop this X-linked syndrome. Many have brothers or uncles with the same disease.

The infections are the result of abnormal B cells and certain T cell functions. Because of B cell defects, these boys cannot make antibodies against some types of bacteria. This leaves them susceptible to ear infections, pneumonias, blood infections, and meningitis. Because of the T cell defects, they are

vulnerable to infections with opportunistic germs, including *Candida*, *Pneumocystis*, and the herpes viruses.

Patients with WAS also have defective blood platelets. Platelets are essential for blood clotting as well as certain immune responses. The platelets of youngsters with WAS are too few and too small. (The size of the platelets confirms the diagnosis.)

The lack of platelets causes bleeding, often for no obvious reason. These patients develop bruises, bleeding gums, prolonged nose bleeds, and bloody bowel movements. They also risk deadly bleeding into the brain.

Eczema in WAS can range from mild to severe. It can cause children to itch and scratch themselves until they bleed. This is aggravated by dry skin. Thus, it is important to identify food allergies that cause the skin to itch. Bath oil, moisturizing and steroid creams, and antibiotics on the skin may help relieve the eczema, but keeping the skin clean is also important.

The leading treatment option for WAS is bone marrow transplantation. When marrow is available from a brother or sister who is an identical match, the cure rate exceeds 85 percent.

To correct severe bleeding, a life-saving alternative may be surgery to remove the spleen. In WAS, the spleen wrongly filters platelets out of the blood. Removing the spleen (a relatively simple operation) allows platelets to remain in the bloodstream and prevents dangerous bleeding. However, removing the spleen makes the patient more susceptible to certain infections (e.g., blood poisoning). Consequently, surgery is rarely used. Conservative measures such as antibiotics, IVIG, and avoidance of allergic foods should be tried before spleen removal or BMT.

At one time, a boy with WAS was unlikely to live past the age of 10. Today, thanks to BMT or surgery to remove the spleen coupled with daily antibiotics or regular IVIG to prevent infections, these youngsters may live relatively normal lives for many years. Freed from the risk of easy bleeding and constant infections, they can ride bikes, play contact sports, and mix freely with other children. Many young men with WAS are now living productive lives in their twenties and thirties.

## **Ataxia-Telangiectasia (AT)**

Ataxia-Telangiectasia (AT) is a PI syndrome that affects several body systems, and the symptoms grow worse with time. Children with AT have nervous system problems that cause them to walk unsteadily and clumsily (ataxia), as well as dilated blood vessels (telangiectasia) in the eyes and skin. They also develop frequent sinus and respiratory infections such as bronchitis and pneumonia.

The infections in AT can be traced to defects in both B cells and T cells. B cell responses are substandard, and levels of IgA and IgG may be low. T cells are few and weak; the thymus gland is immature.

Usually AT is first suspected when a child is learning to walk, and has trouble with balance and coordination. A history of infection may or may not be present. The dilated blood vessels typically don't develop before the age of 3 or 4.

The diagnosis can be confirmed by a blood test showing "fetal proteins." These are substances normally produced during the development of a fetus. When levels remain high after birth, it is usually a sign of certain disorders, including AT.

Children with AT gradually lose more and more control of their muscles, and they may develop writhing and jerking movements. By the time they are in their teens, many are confined to a wheel chair. Their infections multiply, too. In addition, they are liable to develop cancers, especially cancers related to immune system cells and organs.

However, the symptoms and severity of AT differ greatly from one child to another, and the disease develops at a different rate for each one. Some have lived well into adulthood, attending college and living independently.

Medical researchers have tried a number of new approaches, including transplants of thymus tissue and BMT. To date, however, nothing has succeeded in halting the disease's advance.

Treatment is geared to helping the children maintain as normal a lifestyle as possible. They are encouraged to attend school and participate in a wide variety of activities. Physical therapy helps the children remain mobile and active.

Infections, of course, need to be treated promptly. AT in children with an IgG deficiency may benefit from IVIG.

## **T Cell Deficiencies**

### **DiGeorge Anomaly**

DiGeorge Anomaly is the result of a birth defect. In the growing fetus, a group of cells that give rise to various parts of the head and neck develops abnormally. Developmental changes can affect the face, parts of the brain, and the heart, as well as the thymus, where T cells mature.

The symptoms of DiGeorge Anomaly may be different for each child, depending on which organs are abnormally affected. The abnormalities can range from mild to severe.

Some children with DiGeorge Anomaly have a distinctive look, with an underdeveloped chin, eyes that slant downward, and misshapen ear lobes. Some children also have underdeveloped parathyroid glands. The parathyroids, located in the neck next to the thyroid gland, produce a hormone that helps to control levels of calcium in the blood; when calcium levels are not balanced, the child can develop convulsions. Children with DiGeorge Anomaly may also have a variety of heart defects, which causes symptoms ranging from a heart murmur to heart failure.

Many children with DiGeorge Anomaly have a very small thymus that is normal. In others, the thymus is missing altogether. With too few T cells, or T cells that are not functioning properly (which means B cells dependent on T cells aren't functioning, either), the child falls prey to infection.

Because of the unusual mixture of characteristic features, DiGeorge Anomaly is usually diagnosed soon after birth. Laboratory analysis of the chromosomal defects in the child's blood cells can be used to confirm the diagnosis.

Treatments are geared to correcting the various defects. The heart malformation, which is usually the most serious problem, requires drugs and often surgery. The child may be given IVIG to prevent infections and drugs to defend against *Pneumocystis pneumonia*. Other treatments include calcium supplements and parathyroid hormone.

For many children with DiGeorge Anomaly, a tiny thymus will eventually grow big enough to produce enough T cells to stave off infection. About a quarter of all children, though, will require some sort of treatment, and researchers are working to find what works best.

An experimental approach is an identically matched BMT which contains T cells that are mature and thus work independently of a thymus. Another experimental technique being used is the transplantation of fetal thymus tissue.

### **Cartilage Hair Hypoplasia**

Cartilage Hair Hypoplasia is an immune system abnormality linked to dwarfism. The child has abnormally short limbs and thin, sparse hair. The skin forms extra folds around the neck, hands, and feet, and the joints are loose.

Youngsters with Cartilage Hair Hypoplasia can get frequent infections of the skin and mouth, the result of too few T cells. Their biggest danger is chicken pox which can be deadly.

The prognosis is considerably better than most T cell immunodeficiencies, because the susceptibility to infection is less. Although some children succumb to overwhelming infections in infancy, most get relatively few infections and some live normal lives. Some children have been successfully treated with BMT.

## **Defective Phagocytes**

### **Chronic Granulomatous Disease (CGD)**

Chronic Granulomatous Disease (CGD) is the name given to a group of inherited immunodeficiency diseases caused by faulty phagocytes. Normally, these large white blood cells engulf germs and destroy them. In CGD, phagocytes are unable to produce the oxygen-transporting compounds that they need in order to kill certain types of germs.

There are four types of CGD, each caused by a different gene defect. Each of these genes encodes one of four proteins that act together to allow phagocytes to kill germs. One gene is on the X chromosome while the other

three are recessive genes on autosomes. (About two-thirds of the cases occur in boys.)

By their second birthday, most children with CGD will have infections that are unusually frequent or severe. The infections often respond poorly to standard antibiotics, and in some instances the child may need to be hospitalized for prolonged intravenous antibiotic treatment.

A commonplace bacterium such as *Staphylococcus aureus* or a usually harmless fungus such as *Aspergillus* may cause skin infections and rashes, liver abscesses, fever and persistent cough. Almost all the youngsters develop lung disease, including pneumonia. CGD can also cause chronic inflammatory conditions, including gum disease, inflammatory bowel disease, and enlarged lymph glands.

In addition, CGD causes tumor-like masses called granulomas. Granulomas are made up of clusters of white blood cells that continue to collect in infected areas even after the infection is gone. If large and in critical locations, granulomas can obstruct the passage of food through the digestive tract or the flow of urine.

The key to managing CGD is a prompt diagnosis (special blood tests that show how well phagocytes utilize oxygen and how efficiently they kill bacteria) and quick treatment with powerful antibiotics.

Once current infections and granulomas have been brought under control, attention turns to forestalling future infections. Children treated with routine preventive antibiotics can go three or four years between serious infections. The outlook is better yet when they receive regular injections of gamma interferon. This promising new treatment results in many fewer serious infections and shorter hospital stays.

Patients with CGD are encouraged to have frequent checkups, and to see their doctors for even minor infections. It is also important to keep the skin clean because many germs gain entry through the skin.

Thanks to preventive treatments and to prompt and aggressive therapy when infections do occur, the outlook for patients with CGD is good. Although they must guard against serious infections, they can look forward to long periods of good health and long, productive lives.

### **Leukocyte Adhesion Defect (LAD)**

Leukocyte Adhesion Defect (LAD) causes recurrent, life-threatening infections because phagocytes are unable to migrate to the scene of an infection. These phagocytes lack a molecule that allows them to attach to blood vessel walls, a first step in leaving the circulation to enter tissues. Other white cells also lack adhesion molecules, preventing them from attaching to target cells and surfaces.

LAD typically manifests itself in infancy. One of the first signs may be a problem with the baby's umbilical cord; it fails to drop off, in the normal way, within a few weeks. The baby has a very high white blood cell count. Children with LAD are prey to severe infections caused by bacteria and fungi, especially infections of the soft tissues. They get tissue-eroding infections of the skin without forming pus, severe infections of the gums—leading to tooth loss—and infections of the intestinal tract. Wounds heal poorly and may leave scars.

Treatment of LAD begins with early and aggressive therapy of infections with antibiotics. Most recently, LAD has joined the ranks of the other PIs treated successfully with BMT.

### **Chediak-Higashi Syndrome (CHS)**

Chediak-Higashi Syndrome (CHS) is a rare and potentially severe disorder caused by a flaw in three distinct types of cells: phagocytes, platelets, and melanocytes.

Because of the flawed phagocytes, the child has little resistance to frequent and severe infections. In addition to repeated sinus infections and pneumonia, the individual develops infections that infiltrate beneath the skin (cellulitis).

The defective platelets, for their part, result in a mild bleeding disorder.

Melanocytes are cells containing melanin, a pigment that provides color to the skin, hair, and eyes. The skin and hair of a youngster with CHS lack color (partial albinism), while lack of pigment in the eyes makes the person overly sensitive to light.

The infections of CHS are treated aggressively with antibiotics. Ultimately, however, CHS will enter an accelerated phase. The patient develops a

lymphoma-like illness, with fever and jaundice; lymphoid organs such as the spleen fill with T cells that behave like cancer. Despite treatment with steroids and anticancer drugs, the condition is usually fatal within months.

Fortunately, the immunodeficiency of CHS is one more condition that can be cured with BMT. A recent study found a majority of children to be alive and well up to 13 years after BMT treatment.

## **Complement Deficiencies**

For the complement system to function, all of its 20-plus components must work closely together. Yet each of the components can be thrown out of step by a different genetic mutation.

Immunodeficiencies involving the complement system are not common. Often they don't cause disease until adulthood.

Symptoms vary from one type to another. Some complement deficiencies foster the same kinds of bacterial infections seen with antibody deficiencies, as well as immune system disorders such as SLE. Other complement deficiencies lead to an increase of blood-borne infections such as meningitis.

Cure is not possible, and there is no specific therapy for complement deficiencies. However, proper management can usually prevent serious consequences. Sometimes immunization against encapsulated bacteria helps to keep infections in check. Recent investigations are exploring the use of complement concentrates to replace the deficient complement components.

## **Deficiencies/Cause Unknown**

### **Hyper-IgE Syndrome**

Hyper-IgE Syndrome is a relatively rare condition characterized by extremely high (hyper) levels of IgE in the blood. From infancy, children with Hyper-IgE are plagued by severe, recurrent abscesses, especially of the skin and lungs.

Most of the infections in Hyper-IgE are caused by *Staphylococcus aureus*. However, they can be produced by other germs, and they can involve the joints, eyes, ears, nose, sinuses, and blood.



Skin infections typically appear as abscesses on the scalp, face, and neck. They often need to be lanced and drained.

Children with Hyper-IgE Syndrome may have recurrent pneumonias, lung abscesses and often have coarse features, an itchy rash, and skeletal abnormalities, including thin bones prone to repeated fractures. Their growth rate may also be slow.

Because the primary defect is unknown, there is no specific therapy for Hyper-IgE Syndrome. Treatment consists of lifelong antibiotics to combat staphylococcus infections. Other drugs, such as antifungal agents, are given for specific infections. Persons with antibody deficiency may benefit from IVIG.

### **Chronic Mucocutaneous Candidiasis**

Chronic Mucocutaneous Candidiasis is associated with other immunodeficiencies. The patients are unable to defend themselves against the *Candida* fungus. As a result, they develop rashes and sores on the skin, nails, and the mucous membranes.

Within the first few months of life, infants develop persistent thrush, a *Candida* infection of the mucous membranes of the mouth, and *Candida* diaper rash. *Candida* infections on the hands and feet can destroy fingernails and toenails.

Patients with chronic mucocutaneous candidiasis can also get other types of infections. Both bacteria and viruses can infect the skin and the respiratory tracts. In addition, they risk autoimmune blood disorders such as anemia. Many have problems with endocrine glands such as the parathyroid, thyroid, and adrenal glands.

Treatment has two goals: to clear up infections and to cure the underlying immune defect. A variety of antifungal drugs are effective against *Candida*, and it may be necessary to try several—of increasing strength—to find one that works. Sometimes intravenous drugs are necessary.

Unfortunately, the effects of drug treatment don't last. Infections will usually flare up again a few weeks or months after the antifungal drugs are stopped.

## Research In Progress

Research on PIs is under way on many fronts. Geneticists, immunologists, molecular biologists, microbiologists, and biochemists are working to understand fundamental defects and to devise remedies. New genes are being identified, and scientists are making rapid progress in untangling the intricate connections and pathways that govern immune responses. Clinical scientists are developing new treatments to alleviate symptoms and prevent complications.

### Gene Therapy

Gene therapy is one of the most publicized forms of treatment for PI. This revolutionary approach was first used to treat two young girls with SCID due to ADA deficiency.

Gene therapy attempts to cure disease by inserting a healthy version of a missing or malfunctioning gene into a cell to restore normal function. If successful, the newly inserted gene directs the cell to produce the missing protein.

In the pioneering 1990 experiment, some of the girls' T cells were removed, treated to make them more active, and a gene for ADA was introduced. These T cells carrying the new gene were then reinjected into the girls. Meanwhile, these girls still continued to receive their PEG-ADA treatment.

Today, the girls are healthy and free of severe infections. Both of them are attending school and living relatively normal lives.

One of the two girls has had an especially good response. She has some T cells that carry the new gene and produce the ADA enzyme. However, since both girls have always received PEG-ADA, it is not clear how much of the credit for their good health can be attributed to the new genes.

Still more recently, doctors have tried gene therapy using stem cells, which are much longer-lived than T cells. In three different cases, babies were diagnosed with ADA deficiency before they were born. Their own umbilical cord blood was collected, and stem cells taken from the cord blood had new genes inserted. Each of the babies was then given a transfusion of his/her own genetically-engineered stem cells.

These children did well initially. But like the girls given T cell gene therapy, they continue to require other treatments.

Currently, gene therapy remains strictly experimental, and not yet used routinely for therapy.

### **Basic Research Efforts**

The National Institute of Child Health and Human Development (NICHD), part of the National Institutes of Health (NIH), in collaboration with the Jeffrey Modell Foundation (JMF), supports a 5-year basic research initiative on developmental and genetic defects of immunity. The research is exploring the genes and molecular mechanisms that play a role in the development of the immune system in the fetus, newborn, infant, and child. Insights emerging from this basic research will lead to new and better strategies for the diagnosis, treatment, and prevention of PIs. In addition, the NICHD and the National Institute of Allergy and Infectious Diseases (NIAID) sponsor a basic research program on PIs. The objectives are to identify and characterize the genes, and to elucidate the molecular and genetic mechanisms that cause PIs. Moreover, the NIAID and the JMF support basic research studies to develop gene transfer methods for correcting the genetic defects of PIs.

### **Registries**

The NIAID, working with the Immune Deficiency Foundation, has established a registry of patients with CGD. The Registry will allow researchers to gather data on hundreds of patients being enrolled. Early indications from the Registry show that CGD may be four times more common than previously thought.

A similar registry supported by the NIAID has been established at the Immune Deficiency Foundation for patients with eight different types of PIs.

### **Future Research Challenges**

Since there are many different types of PIs, they present a formidable research challenge to the scientific community. However, thanks to the timely and extraordinary advances of genetics, molecular biology, and molecular medicine, the challenge can be met and conquered. Already these exciting new scientific tools have unraveled many of the mysteries behind

the PIs, and have significantly increased our insight and basic understanding of them. Moreover, they have contributed to the development of new and improved approaches and strategies to diagnose, treat, and prevent PIs.

A major challenge is to identify the genes that cause PIs and characterize the nature of each genetic defect and its associated immunodeficiency disease. More than 70 PI genes have already been identified and characterized. With more advances in genetic technology and rapid molecular analytical methods, progress on defective gene identification and characterization should accelerate.

Although gammaglobulin therapy, bone marrow transplantation, gamma interferon, and PEG-ADA have been effective for treating specific forms of PI, new and emerging opportunities for improving these therapies show great promise. In addition, research into using gene therapy will continue to improve the prognosis of patients with PIs. Finally, an important research challenge is to develop new and innovative treatments that are more efficacious, easier to administer, less costly, and that allow the patient to lead a normal lifestyle.

## Resources

Information on basic and clinical research on PI diseases is available from the NIH institutes listed below. For information on the diagnosis, treatment, and clinical care of patients with PI, consult your pediatrician or family physician. Additional information may be obtained from the two PI organizations listed below. They are valuable resources for information on research, referral centers, physician and patient education, patient support, and public awareness of PIs.

### **National Institutes of Health**

#### **National Institute of Child Health and Human Development, NIH**

Public Information and Communications Branch

31 Center Drive, Room 2A32

Bethesda, MD 20892-2425

301-496-5133

<http://www.nih.gov/nichd/>

**National Human Genome Research Institute, NIH**

Information Office

31 Center Drive, Room 4B09

Bethesda, MD 20892-2152

301-402-0911

**National Institute of Allergy and Infectious Diseases, NIH**

Office of Communications

31 Center Drive, Room 7A50

Bethesda, MD 20892-2520

301-496-5717

**National Heart, Lung, and Blood Institute Information Center, NIH**

Post Office Box 30105

Bethesda, MD 20824-0105

301-251-1222

**Other Organizations**

Expert information and advice are available from two national organizations that focus specifically on PIs.

The Jeffrey Modell Foundation is a nonprofit research foundation devoted to PI. It sponsors symposia and workshops; supports research and training; and provides diagnostic, clinical, and education services. Its 24-hour-a-day national hotline, which offers information and referrals to immunologists at major medical centers around the country, can be reached at 1-800-JEFF-844. Its Internet Home Page can be accessed at <http://www.jmfworld.com>. Its E-mail address is [info@jmfworld.com](mailto:info@jmfworld.com).

The Immune Deficiency Foundation, a non-profit foundation, has chapters nationwide to serve patients, families and medical professionals dealing with the PI diseases. It supports scientific research and training and fosters public education. Immune Deficiency Foundation publications include a Patient Handbook and a National Newsletter. The Patient Support Line can be reached at 1-800-296-4433. Its Internet Home Page can be accessed at <http://www.primaryimmune.org>. Its e-mail address is [idf@clark.net](mailto:idf@clark.net).

## More Guideline Sources

The guideline above on primary immunodeficiency is only one example of the kind of material that you can find online and free of charge. The remainder of this chapter will direct you to other sources which either publish or can help you find additional guidelines on topics related to primary immunodeficiency. Many of the guidelines listed below address topics that may be of particular relevance to your child's specific situation, while certain guidelines will apply to only some children with primary immunodeficiency. Due to space limitations these sources are listed in a concise manner. Do not hesitate to consult the following sources by either using the Internet hyperlink provided, or, in cases where the contact information is provided, contacting the publisher or author directly.

### Topic Pages: MEDLINEplus

For parents wishing to go beyond guidelines published by specific Institutes of the NIH, the National Library of Medicine has created a vast and parent-oriented healthcare information portal called MEDLINEplus. Within this Internet-based system are "health topic pages." You can think of a health topic page as a guide to patient guides. To access this system, log on to **<http://www.nlm.nih.gov/medlineplus/healthtopics.html>**. From there you can either search using the alphabetical index or browse by broad topic areas.

If you do not find topics of interest when browsing health topic pages, then you can choose to use the advanced search utility of MEDLINEplus at **<http://www.nlm.nih.gov/medlineplus/advancedsearch.html>**. This utility is similar to the NIH Search Utility, with the exception that it only includes material linked within the MEDLINEplus system (mostly parent-oriented information). It also has the disadvantage of generating unstructured results. We recommend, therefore, that you use this method only if you have a very targeted search.

### The Combined Health Information Database (CHID)

CHID Online is a reference tool that maintains a database directory of thousands of journal articles and educational guidelines on primary immunodeficiency and related conditions. One of the advantages of CHID over other sources is that it offers summaries that describe the guidelines available, including contact information and pricing. CHID's general Web

site is <http://chid.nih.gov/>. To search this database, go to <http://chid.nih.gov/detail/detail.html>. In particular, you can use the advanced search options to look up pamphlets, reports, brochures, and information kits. The following was recently posted in this archive:

- **Primary Immune Deficiency Diseases: An Overview**

Source: Ellicott City, MD: Immune Deficiency Foundation (IDF). 1988. [12 p.].

Contact: Available from Immune Deficiency Foundation (IDF). 25 West Chesapeake Avenue, Suite 206, Towson, MD 21204. (410) 321-6647 or (800) 296-4433; FAX (410) 321-9165. PRICE: \$0.25.

Summary: This brochure describes the function of the immune system and presents an overview of primary immunodeficiency diseases, their causes, symptoms, and the diagnostic tests used to evaluate the functions of the immune system. Treatments such as gamma globulin injections, bone marrow transplantation, drug therapy, and infection therapy are discussed. The brochure also discusses the prognosis for patients with immunodeficiency diseases, future directions in immune deficiency disease research, and the goals and activities of the Immune Deficiency Foundation.

### **The National Guideline Clearinghouse™**

The National Guideline Clearinghouse™ offers hundreds of evidence-based clinical practice guidelines published in the United States and other countries. You can search their site located at <http://www.guideline.gov> by using the keyword “primary immunodeficiency” or synonyms. The following was recently posted:

- **Measles, mumps, and rubella: vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps. Recommendations of the Advisory Committee on Immunization Practices (ACIP). Notice to readers: Revised ACIP recommendation for avoiding pregnancy after receiving a rubella-containing vaccine.**

Source: Centers for Disease Control and Prevention.; 1998 May 22; 45 pages

[http://www.guideline.gov/FRAMESETS/guideline\\_fs.asp?guideline=001604&sSearch\\_string=primary+immunodeficiency](http://www.guideline.gov/FRAMESETS/guideline_fs.asp?guideline=001604&sSearch_string=primary+immunodeficiency)

- **Prevention and treatment of tuberculosis among patients with infected human immunodeficiency virus: Principles of therapy and revised recommendations. Notice to readers: updated guidelines for the use of rifabutin or rifampin for the treatment and prevention of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors.**

Source: Centers for Disease Control and Prevention.; 1998 October 30 (updated 2000 Mar); 59 pages

[http://www.guideline.gov/FRAMESETS/guideline\\_fs.asp?guideline=001383&sSearch\\_string=primary+immunodeficiency](http://www.guideline.gov/FRAMESETS/guideline_fs.asp?guideline=001383&sSearch_string=primary+immunodeficiency)

- **Targeted tuberculin testing and treatment of latent tuberculosis infection. Update: fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC recommendations - United States, 2001.**

Source: Centers for Disease Control and Prevention.; 2000 June 9; 54 pages

[http://www.guideline.gov/FRAMESETS/guideline\\_fs.asp?guideline=001528&sSearch\\_string=primary+immunodeficiency](http://www.guideline.gov/FRAMESETS/guideline_fs.asp?guideline=001528&sSearch_string=primary+immunodeficiency)

- **2001 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus.**

Source: Centers for Disease Control and Prevention/Infectious Diseases Society of America/Public Health Service (U.S.); 1999 August (updated 2001 November 28); 64 pages

[http://www.guideline.gov/FRAMESETS/guideline\\_fs.asp?guideline=002306&sSearch\\_string=primary+immunodeficiency](http://www.guideline.gov/FRAMESETS/guideline_fs.asp?guideline=002306&sSearch_string=primary+immunodeficiency)

- **AACE/ACE position statement on the prevention, diagnosis and treatment of obesity.**

Source: American Association of Clinical Endocrinologists/American College of Endocrinology.; 1997 (revised 1998); 35 pages

[http://www.guideline.gov/FRAMESETS/guideline\\_fs.asp?guideline=000976&sSearch\\_string=primary+immunodeficiency](http://www.guideline.gov/FRAMESETS/guideline_fs.asp?guideline=000976&sSearch_string=primary+immunodeficiency)



- **AAFP summary of policy recommendations for periodic health examination. (Revision 5.1).**

Source: American Academy of Family Physicians.; 1996 August (revised 2001 Dec); 15 pages

[http://www.guideline.gov/FRAMESETS/guideline\\_fs.asp?guideline=002379&sSearch\\_string=primary+immunodeficiency](http://www.guideline.gov/FRAMESETS/guideline_fs.asp?guideline=002379&sSearch_string=primary+immunodeficiency)

- **ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure).**

Source: American College of Cardiology/American Heart Association.; 1995 November 1 (revised 2001 Dec); 56 pages

[http://www.guideline.gov/FRAMESETS/guideline\\_fs.asp?guideline=002340&sSearch\\_string=primary+immunodeficiency](http://www.guideline.gov/FRAMESETS/guideline_fs.asp?guideline=002340&sSearch_string=primary+immunodeficiency)

- **ACR Appropriateness Criteria™ for needle biopsy in the thorax.**

Source: American College of Radiology.; 1996 (revised 1999); 12 pages

[http://www.guideline.gov/FRAMESETS/guideline\\_fs.asp?guideline=001724&sSearch\\_string=primary+immunodeficiency](http://www.guideline.gov/FRAMESETS/guideline_fs.asp?guideline=001724&sSearch_string=primary+immunodeficiency)

- **Acute pharyngitis.**

Source: Institute for Clinical Systems Improvement.; 1998 August (revised 2000 Jun); 24 pages

[http://www.guideline.gov/FRAMESETS/guideline\\_fs.asp?guideline=001977&sSearch\\_string=primary+immunodeficiency](http://www.guideline.gov/FRAMESETS/guideline_fs.asp?guideline=001977&sSearch_string=primary+immunodeficiency)

- **Acute rhinosinusitis in adults.**

Source: University of Michigan Health System.; 1996 May (revised 1999 Dec); 7 pages

[http://www.guideline.gov/FRAMESETS/guideline\\_fs.asp?guideline=001511&sSearch\\_string=primary+immunodeficiency](http://www.guideline.gov/FRAMESETS/guideline_fs.asp?guideline=001511&sSearch_string=primary+immunodeficiency)

### **Healthfinder™**

Healthfinder™ is an additional source sponsored by the U.S. Department of Health and Human Services which offers links to hundreds of other sites that contain healthcare information. This Web site is located at **<http://www.healthfinder.gov>**. Again, keyword searches can be used to find guidelines. The following was recently found in this database:

- **Primary Immunodeficiency Diseases**

Summary: Primary immunodeficiency diseases are a group of diseases in which immune system malfunction causes increased susceptibility to infection, autoimmune diseases, and malignancy.

Source: National Institute of Allergy and Infectious Diseases, National Institutes of Health

<http://www.healthfinder.gov/scripts/recordpass.asp?RecordType=0&RecordID=3771>

### **The NIH Search Utility**

After browsing the references listed at the beginning of this chapter, you may want to explore the NIH Search Utility. This allows you to search for documents on over 100 selected Web sites that comprise the NIH-WEB-SPACE. Each of these servers is “crawled” and indexed on an ongoing basis. Your search will produce a list of various documents, all of which will relate in some way to primary immunodeficiency. The drawbacks of this approach are that the information is not organized by theme and that the references are often a mix of information for professionals and parents. Nevertheless, a large number of the listed Web sites provide useful background information. We can only recommend this route, therefore, for relatively rare or specific disorders, or when using highly targeted searches. To use the NIH search utility, visit the following Web page: **<http://search.nih.gov/index.html>**.

## Additional Web Sources

A number of Web sites that often link to government sites are available to the public. These can also point you in the direction of essential information. The following is a representative sample:

- AOL: <http://search.aol.com/cat.adp?id=168&layer=&from=subcats>
- drkoop.com<sup>®</sup>: <http://www.drkoop.com/conditions/ency/index.html>
- Family Village: <http://www.familyvillage.wisc.edu/specific.htm>
- Google:  
[http://directory.google.com/Top/Health/Conditions\\_and\\_Diseases/](http://directory.google.com/Top/Health/Conditions_and_Diseases/)
- Med Help International: <http://www.medhelp.org/HealthTopics/A.html>
- Open Directory Project:  
[http://dmoz.org/Health/Conditions\\_and\\_Diseases/](http://dmoz.org/Health/Conditions_and_Diseases/)
- Yahoo.com: [http://dir.yahoo.com/Health/Diseases\\_and\\_Conditions/](http://dir.yahoo.com/Health/Diseases_and_Conditions/)
- WebMD<sup>®</sup>Health: [http://my.webmd.com/health\\_topics](http://my.webmd.com/health_topics)

## Vocabulary Builder

The material in this chapter may have contained a number of unfamiliar words. The following Vocabulary Builder introduces you to terms used in this chapter that have not been covered in the previous chapter:

**Adenosine:** A nucleoside that is composed of adenine and d-ribose. Adenosine or adenosine derivatives play many important biological roles in addition to being components of DNA and RNA. Adenosine itself is a neurotransmitter. [NIH]

**Agammaglobulinemia:** An immunologic deficiency state characterized by an extremely low level of generally all classes of gamma-globulin in the blood. [NIH]

**Albinism:** General term for a number of inherited defects of amino acid metabolism in which there is a deficiency or absence of pigment in the eyes, skin, or hair. [NIH]

**Amniocentesis:** Percutaneous transabdominal puncture of the uterus during pregnancy to obtain amniotic fluid. It is commonly used for fetal karyotype determination in order to diagnose abnormal fetal conditions. [NIH]

**Anemia:** A reduction in the number of circulating erythrocytes or in the quantity of hemoglobin. [NIH]

**Anesthesia:** A state characterized by loss of feeling or sensation. This depression of nerve function is usually the result of pharmacologic action and is induced to allow performance of surgery or other painful procedures. [NIH]

**Antibiotic:** A chemical substance produced by a microorganism which has the capacity, in dilute solutions, to inhibit the growth of or to kill other microorganisms. Antibiotics that are sufficiently nontoxic to the host are used as chemotherapeutic agents in the treatment of infectious diseases of man, animals and plants. [EU]

**Antibody:** An immunoglobulin molecule that has a specific amino acid sequence by virtue of which it interacts only with the antigen that induced its synthesis in cells of the lymphoid series (especially plasma cells), or with antigen closely related to it. Antibodies are classified according to their mode of action as agglutinins, bacteriolysins, haemolysins, opsonins, precipitins, etc. [EU]

**Antifungal:** Destructive to fungi, or suppressing their reproduction or growth; effective against fungal infections. [EU]

**Antigen:** Any substance which is capable, under appropriate conditions, of inducing a specific immune response and of reacting with the products of that response, that is, with specific antibody or specifically sensitized T-lymphocytes, or both. Antigens may be soluble substances, such as toxins and foreign proteins, or particulate, such as bacteria and tissue cells; however, only the portion of the protein or polysaccharide molecule known as the antigenic determinant (q.v.) combines with antibody or a specific receptor on a lymphocyte. Abbreviated Ag. [EU]

**Antimicrobial:** Killing microorganisms, or suppressing their multiplication or growth. [EU]

**Aspergillus:** A genus of mitosporic fungi containing about 100 species and eleven different teleomorphs in the family Trichocomaceae. [NIH]

**Ataxia:** Failure of muscular coordination; irregularity of muscular action. [EU]

**Bacteria:** Unicellular prokaryotic microorganisms which generally possess rigid cell walls, multiply by cell division, and exhibit three principal forms: round or coccid, rodlike or bacillary, and spiral or spirochetal. [NIH]

**Biopsy:** The removal and examination, usually microscopic, of tissue from the living body, performed to establish precise diagnosis. [EU]

**Bronchial:** Pertaining to one or more bronchi. [EU]

**Bronchitis:** Inflammation of one or more bronchi. [EU]

**Candidiasis:** Infection with a fungus of the genus *Candida*. It is usually a superficial infection of the moist cutaneous areas of the body, and is

generally caused by *C. albicans*; it most commonly involves the skin (dermatocandidiasis), oral mucous membranes (thrush, def. 1), respiratory tract (bronchocandidiasis), and vagina (vaginitis). Rarely there is a systemic infection or endocarditis. Called also moniliasis, candidosis, oidiomycosis, and formerly blastodendriosis. [EU]

**Capsules:** Hard or soft soluble containers used for the oral administration of medicine. [NIH]

**Cardiology:** The study of the heart, its physiology, and its functions. [NIH]

**Cellulitis:** An acute, diffuse, and suppurative inflammation of loose connective tissue, particularly the deep subcutaneous tissues, and sometimes muscle, which is most commonly seen as a result of infection of a wound, ulcer, or other skin lesions. [NIH]

**Convulsion:** A violent involuntary contraction or series of contractions of the voluntary muscles. [EU]

**Cryptococcus:** A mitosporic Tremellales fungal genus whose species usually have a capsule and do not form pseudomycellium. Teleomorphs include *Filobasidiella* and *Fidobasidium*. [NIH]

**Cryptosporidium:** A genus of coccidian parasites of the family cryptosporidiidae, found in the intestinal epithelium of many vertebrates including humans. [NIH]

**Cytokines:** Non-antibody proteins secreted by inflammatory leukocytes and some non-leukocytic cells, that act as intercellular mediators. They differ from classical hormones in that they are produced by a number of tissue or cell types rather than by specialized glands. They generally act locally in a paracrine or autocrine rather than endocrine manner. [NIH]

**Cytomegalovirus:** A genus of the family herpesviridae, subfamily betaherpesvirinae, infecting the salivary glands, liver, spleen, lungs, eyes, and other organs, in which they produce characteristically enlarged cells with intranuclear inclusions. Infection with Cytomegalovirus is also seen as an opportunistic infection in AIDS. [NIH]

**Cytotoxic:** Pertaining to or exhibiting cytotoxicity. [EU]

**Diphtheria:** A localized infection of mucous membranes or skin caused by toxigenic strains of *Corynebacterium diphtheriae*. It is characterized by the presence of a pseudomembrane at the site of infection. Diphtheria toxin, produced by *C. diphtheriae*, can cause myocarditis, polyneuritis, and other systemic toxic effects. [NIH]

**Eczema:** A pruritic papulovesicular dermatitis occurring as a reaction to many endogenous and exogenous agents, characterized in the acute stage by erythema, edema associated with a serous exudate between the cells of the epidermis (spongiosis) and an inflammatory infiltrate in the dermis, oozing

and vesiculation, and crusting and scaling; and in the more chronic stages by lichenification or thickening or both, signs of excoriations, and hyperpigmentation or hypopigmentation or both. Atopic dermatitis is the most common type of dermatitis. Called also eczematous dermatitis. [EU]

**Encephalitis:** Inflammation of the brain. [EU]

**Endocrinology:** A subspecialty of internal medicine concerned with the metabolism, physiology, and disorders of the endocrine system. [NIH]

**Enzyme:** A protein molecule that catalyses chemical reactions of other substances without itself being destroyed or altered upon completion of the reactions. Enzymes are classified according to the recommendations of the Nomenclature Committee of the International Union of Biochemistry. Each enzyme is assigned a recommended name and an Enzyme Commission (EC) number. They are divided into six main groups; oxidoreductases, transferases, hydrolases, lyases, isomerases, and ligases. [EU]

**Esophagitis:** Inflammation, acute or chronic, of the esophagus caused by bacteria, chemicals, or trauma. [NIH]

**Expectorant:** 1. promoting the ejection, by spitting, of mucus or other fluids from the lungs and trachea. 2. an agent that promotes the ejection of mucus or exudate from the lungs, bronchi, and trachea; sometimes extended to all remedies that quiet cough (antitussives). [EU]

**Fatigue:** The state of weariness following a period of exertion, mental or physical, characterized by a decreased capacity for work and reduced efficiency to respond to stimuli. [NIH]

**Fibrosis:** The formation of fibrous tissue; fibroid or fibrous degeneration [EU]

**Fungus:** A general term used to denote a group of eukaryotic protists, including mushrooms, yeasts, rusts, moulds, smuts, etc., which are characterized by the absence of chlorophyll and by the presence of a rigid cell wall composed of chitin, mannans, and sometimes cellulose. They are usually of simple morphological form or show some reversible cellular specialization, such as the formation of pseudoparenchymatous tissue in the fruiting body of a mushroom. The dimorphic fungi grow, according to environmental conditions, as moulds or yeasts. [EU]

**Giardia:** A genus of flagellate intestinal protozoa parasitic in various vertebrates, including humans. Characteristics include the presence of four pairs of flagella arising from a complicated system of axonemes and cysts that are ellipsoidal to ovoidal in shape. [NIH]

**Granulocytes:** Leukocytes with abundant granules in the cytoplasm. They are divided into three groups: neutrophils, eosinophils, and basophils. [NIH]

**Haemophilus:** A genus of pasteurellaceae that consists of several species occurring in animals and humans. Its organisms are described as gram-

negative, facultatively anaerobic, coccobacillus or rod-shaped, and nonmotile. [NIH]

**Herpes:** Any inflammatory skin disease caused by a herpesvirus and characterized by the formation of clusters of small vesicles. When used alone, the term may refer to herpes simplex or to herpes zoster. [EU]

**Hypoplasia:** Incomplete development or underdevelopment of an organ or tissue. [EU]

**Ibuprofen:** A nonsteroidal anti-inflammatory agent with analgesic properties used in the therapy of rheumatism and arthritis. [NIH]

**Immunity:** The condition of being immune; the protection against infectious disease conferred either by the immune response generated by immunization or previous infection or by other nonimmunologic factors (innate i.). [EU]

**Inflammation:** A pathological process characterized by injury or destruction of tissues caused by a variety of cytologic and chemical reactions. It is usually manifested by typical signs of pain, heat, redness, swelling, and loss of function. [NIH]

**Influenza:** An acute viral infection involving the respiratory tract. It is marked by inflammation of the nasal mucosa, the pharynx, and conjunctiva, and by headache and severe, often generalized, myalgia. [NIH]

**Infusion:** The therapeutic introduction of a fluid other than blood, as saline solution, solution, into a vein. [EU]

**Insulin:** A protein hormone secreted by beta cells of the pancreas. Insulin plays a major role in the regulation of glucose metabolism, generally promoting the cellular utilization of glucose. It is also an important regulator of protein and lipid metabolism. Insulin is used as a drug to control insulin-dependent diabetes mellitus. [NIH]

**Intestines:** The section of the alimentary canal from the stomach to the anus. It includes the large intestine and small intestine. [NIH]

**Jaundice:** A clinical manifestation of hyperbilirubinemia, consisting of deposition of bile pigments in the skin, resulting in a yellowish staining of the skin and mucous membranes. [NIH]

**Lobe:** A more or less well-defined portion of any organ, especially of the brain, lungs, and glands. Lobes are demarcated by fissures, sulci, connective tissue, and by their shape. [EU]

**Lupus:** A form of cutaneous tuberculosis. It is seen predominantly in women and typically involves the nasal, buccal, and conjunctival mucosa. [NIH]

**Lymphoma:** Any neoplastic disorder of the lymphoid tissue, the term lymphoma often is used alone to denote malignant lymphoma. [EU]

**Malformation:** A morphologic defect resulting from an intrinsically abnormal developmental process. [EU]

**Manifest:** Being the part or aspect of a phenomenon that is directly observable : concretely expressed in behaviour. [EU]

**Melanocytes:** Epidermal dendritic pigment cells which control long-term morphological color changes by alteration in their number or in the amount of pigment they produce and store in the pigment containing organelles called melanosomes. Melanophores are larger cells which do not exist in mammals. [NIH]

**Membrane:** A thin layer of tissue which covers a surface, lines a cavity or divides a space or organ. [EU]

**Meningitis:** Inflammation of the meninges. When it affects the dura mater, the disease is termed pachymeningitis; when the arachnoid and pia mater are involved, it is called leptomeningitis, or meningitis proper. [EU]

**Molecular:** Of, pertaining to, or composed of molecules : a very small mass of matter. [EU]

**Monocytes:** Large, phagocytic mononuclear leukocytes produced in the vertebrate bone marrow and released into the blood; contain a large, oval or somewhat indented nucleus surrounded by voluminous cytoplasm and numerous organelles. [NIH]

**Mononucleosis:** The presence of an abnormally large number of mononuclear leucocytes (monocytes) in the blood. The term is often used alone to refer to infectious mononucleosis. [EU]

**Mucocutaneous:** Pertaining to or affecting the mucous membrane and the skin. [EU]

**Mucus:** The free slime of the mucous membranes, composed of secretion of the glands, along with various inorganic salts, desquamated cells, and leucocytes. [EU]

**Mycoplasma:** A genus of gram-negative, facultatively anaerobic bacteria bounded by a plasma membrane only. Its organisms are parasites and pathogens, found on the mucous membranes of humans, animals, and birds. [NIH]

**Neurologic:** Pertaining to neurology or to the nervous system. [EU]

**Neutrophil:** Having an affinity for neutral dyes. [EU]

**Oral:** Pertaining to the mouth, taken through or applied in the mouth, as an oral medication or an oral thermometer. [EU]

**Osteomyelitis:** Inflammation of bone caused by a pyogenic organism. It may remain localized or may spread through the bone to involve the marrow, cortex, cancellous tissue, and periosteum. [EU]



**Pancreas:** A mixed exocrine and endocrine gland situated transversely across the posterior abdominal wall in the epigastric and hypochondriac regions. The endocrine portion is comprised of the islets of langerhans, while the exocrine portion is a compound acinar gland that secretes digestive enzymes. [NIH]

**Paralysis:** Loss or impairment of motor function in a part due to lesion of the neural or muscular mechanism; also by analogy, impairment of sensory function (sensory paralysis). In addition to the types named below, paralysis is further distinguished as traumatic, syphilitic, toxic, etc., according to its cause; or as obturator, ulnar, etc., according to the nerve part, or muscle specially affected. [EU]

**Parathyroid:** 1. situated beside the thyroid gland. 2. one of the parathyroid glands. 3. a sterile preparation of the water-soluble principle(s) of the parathyroid glands, administered parenterally as an antihypocalcaemic, especially in the treatment of acute hypoparathyroidism with tetany. [EU]

**Phosphorylase:** An enzyme of the transferase class that catalyzes the phosphorylysis of a terminal alpha-1,4-glycosidic bond at the non-reducing end of a glycogen molecule, releasing a glucose 1-phosphate residue. Phosphorylase should be qualified by the natural substance acted upon. EC 2.4.1.1. [NIH]

**Placenta:** A highly vascular fetal organ through which the fetus absorbs oxygen and other nutrients and excretes carbon dioxide and other wastes. It begins to form about the eighth day of gestation when the blastocyst adheres to the decidua. [NIH]

**Poisoning:** A condition or physical state produced by the ingestion, injection or inhalation of, or exposure to a deleterious agent. [NIH]

**Polyethylene:** A vinyl polymer made from ethylene. It can be branched or linear. Branched or low-density polyethylene is tough and pliable but not to the same degree as linear polyethylene. Linear or high-density polyethylene has a greater hardness and tensile strength. Polyethylene is used in a variety of products, including implants and prostheses. [NIH]

**Proteins:** Polymers of amino acids linked by peptide bonds. The specific sequence of amino acids determines the shape and function of the protein. [NIH]

**Pyrazinamide:** A pyrazine that is used therapeutically as an antitubercular agent. [NIH]

**Radiology:** A specialty concerned with the use of x-ray and other forms of radiant energy in the diagnosis and treatment of disease. [NIH]

**Rifabutin:** A broad-spectrum antibiotic that is being used as prophylaxis against disseminated Mycobacterium avium complex infection in HIV-positive patients. [NIH]

**Rubella:** An acute, usually benign, infectious disease caused by a togavirus and most often affecting children and nonimmune young adults, in which the virus enters the respiratory tract via droplet nuclei and spreads to the lymphatic system. It is characterized by a slight cold, sore throat, and fever, followed by enlargement of the postauricular, suboccipital, and cervical lymph nodes, and the appearances of a fine pink rash that begins on the head and spreads to become generalized. Called also German measles, roetln, röteln, and three-day measles, and rubeola in French and Spanish. [EU]

**Saliva:** The clear, viscous fluid secreted by the salivary glands and mucous glands of the mouth. It contains mucins, water, organic salts, and ptylin. [NIH]

**Secretion:** 1. the process of elaborating a specific product as a result of the activity of a gland; this activity may range from separating a specific substance of the blood to the elaboration of a new chemical substance. 2. any substance produced by secretion. [EU]

**Seizures:** Clinical or subclinical disturbances of cortical function due to a sudden, abnormal, excessive, and disorganized discharge of brain cells. Clinical manifestations include abnormal motor, sensory and psychic phenomena. Recurrent seizures are usually referred to as epilepsy or "seizure disorder." [NIH]

**Serum:** The clear portion of any body fluid; the clear fluid moistening serous membranes. 2. blood serum; the clear liquid that separates from blood on clotting. 3. immune serum; blood serum from an immunized animal used for passive immunization; an antiserum; antitoxin, or antivenin. [EU]

**Sinusitis:** Inflammation of a sinus. The condition may be purulent or nonpurulent, acute or chronic. Depending on the site of involvement it is known as ethmoid, frontal, maxillary, or sphenoid sinusitis. [EU]

**Spectrum:** A charted band of wavelengths of electromagnetic vibrations obtained by refraction and diffraction. By extension, a measurable range of activity, such as the range of bacteria affected by an antibiotic (antibacterial s.) or the complete range of manifestations of a disease. [EU]

**Staphylococcus:** A genus of gram-positive, facultatively anaerobic, coccoid bacteria. Its organisms occur singly, in pairs, and in tetrads and characteristically divide in more than one plane to form irregular clusters. Natural populations of Staphylococcus are membranes of warm-blooded animals. Some species are opportunistic pathogens of humans and animals. [NIH]

**Streptococcus:** A genus of gram-positive, coccoid bacteria whose organisms occur in pairs or chains. No endospores are produced. Many species exist as commensals or parasites on man or animals with some being highly pathogenic. A few species are saprophytes and occur in the natural environment. [NIH]

**Tetanus:** A disease caused by tetanospasmin, a powerful protein toxin produced by *Clostridium tetani*. Tetanus usually occurs after an acute injury, such as a puncture wound or laceration. Generalized tetanus, the most common form, is characterized by tetanic muscular contractions and hyperreflexia. Localized tetanus presents itself as a mild condition with manifestations restricted to muscles near the wound. It may progress to the generalized form. [NIH]

**Toxin:** A poison; frequently used to refer specifically to a protein produced by some higher plants, certain animals, and pathogenic bacteria, which is highly toxic for other living organisms. Such substances are differentiated from the simple chemical poisons and the vegetable alkaloids by their high molecular weight and antigenicity. [EU]

**Toxoplasma:** A genus of protozoa parasitic to birds and mammals. *T. gondii* is one of the most common infectious pathogenic animal parasites of man. [NIH]

**Toxoplasmosis:** An acute or chronic, widespread disease of animals and humans caused by the obligate intracellular protozoon *Toxoplasma gondii*, transmitted by oocysts containing the pathogen in the feces of cats (the definitive host), usually by contaminated soil, direct exposure to infected feces, tissue cysts in infected meat, or tachyzoites (proliferating forms) in blood. [EU]

**Transfusion:** The introduction of whole blood or blood component directly into the blood stream. [EU]

**Transplantation:** The grafting of tissues taken from the patient's own body or from another. [EU]

**Tuberculosis:** Any of the infectious diseases of man and other animals caused by species of *Mycobacterium*. [NIH]

**Uterus:** The hollow muscular organ in female mammals in which the fertilized ovum normally becomes embedded and in which the developing embryo and fetus is nourished. In the nonpregnant human, it is a pear-shaped structure; about 3 inches in length, consisting of a body, fundus, isthmus, and cervix. Its cavity opens into the vagina below, and into the uterine tube on either side at the cornu. It is supported by direct attachment to the vagina and by indirect attachment to various other nearby pelvic structures. Called also metra. [EU]

**Vaccine:** A suspension of attenuated or killed microorganisms (bacteria, viruses, or rickettsiae), administered for the prevention, amelioration or treatment of infectious diseases. [EU]

**Varicella:** Chicken pox. [EU]

**Viral:** Pertaining to, caused by, or of the nature of virus. [EU]

**Viruses:** Minute infectious agents whose genomes are composed of DNA or RNA, but not both. They are characterized by a lack of independent metabolism and the inability to replicate outside living host cells. [NIH]

**Yeasts:** A general term for single-celled rounded fungi that reproduce by budding. Brewers' and bakers' yeasts are *saccharomyces cerevisiae*; therapeutic dried yeast is yeast, dried. [NIH]

## CHAPTER 2. SEEKING GUIDANCE

### Overview

Some parents are comforted by the knowledge that a number of organizations dedicate their resources to helping people with primary immunodeficiency. These associations can become invaluable sources of information and advice. Many associations offer parent support, financial assistance, and other important services. Furthermore, healthcare research has shown that support groups often help people to better cope with their conditions.<sup>9</sup> In addition to support groups, your child's physician can be a valuable source of guidance and support.

In this chapter, we direct you to resources that can help you find parent organizations and medical specialists. We begin by describing how to find associations and parent groups that can help you better understand and cope with your child's condition. The chapter ends with a discussion on how to find a doctor that is right for your child.

### Associations and Primary Immunodeficiency

In addition to associations or groups that your child's doctor might recommend, we suggest that you consider the following list (if there is a fee for an association, you may want to check with your child's insurance provider to find out if the cost will be covered):

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<sup>9</sup> Churches, synagogues, and other houses of worship might also have groups that can offer you the social support you need.

- **American Academy of Allergy Asthma and Immunology**

Address: American Academy of Allergy Asthma and Immunology 611 East Wells Street, Milwaukee, WI 53202

Telephone: (414) 272-6071 Toll-free: (800) 822-2762

Fax: (414) 276-3349

Email: [info@aaaai.org](mailto:info@aaaai.org)

Web Site: <http://www.aaaai.org>

Background: The American Academy of Allergy, Asthma and Immunology (AAAAI) is an international, not-for-profit professional medical specialty organization representing allergists, clinical immunologists, allied health professionals, and other physicians with a special interest in allergy and immunology. Established in 1943 by the merger of the American Association for the Study of Allergy and the Association for the Study of Asthma and Allied Conditions, the AAAAI is dedicated to advancing the knowledge and practice of allergy, fostering the education of students and the public, encouraging union and cooperation among those working in the field, and promoting and stimulating research and the study of allergic diseases. The AAAAI is currently organized into several major 'interest sections' consisting of Asthma, Rhinitis, and Other Respiratory Diseases; Basic and Clinical Immunology; Dermatologic Diseases; Environmental and Occupational Disorders; Food and Drug Reactions and Anaphylaxis; and Mechanisms of Allergy. The AAAAI also engages in patient advocacy and lobbying activities, provides physician referrals, engages in patient education, and provides a variety of informational materials. The Academy currently has more than 5,400 members in the United States, Canada, and over 40 additional countries.

- **Ataxia-Telangiectasia Society (UK)**

Address: Ataxia-Telangiectasia Society (UK) IACR- Rothamsted, Harpenden, Hertfordshire, AL5 2JQ, United Kingdom

Telephone: 01582-760733 Toll-free: (800) 822-2762

Fax: 01582-760162

Email: [ATCharity@aol.com](mailto:ATCharity@aol.com)

Web Site: Non

Background: The Ataxia-Telangiectasia (A-T) Society is a registered charity in the United Kingdom dedicated to providing support and information to individuals and families affected by Ataxia-telangiectasia. Ataxia-telangiectasia is a rare inherited progressive disorder

characterized by an impaired ability to control voluntary movements (ataxia); rapid, involuntary eye movements (nystagmus); permanent dilation of certain small blood vessels, resulting in small red lesions on the skin and other areas (telangiectasias); and primary immune deficiency, causing an increased predisposition to certain bacterial infections and malignancies. The A-T Society raises funds for research into the possible treatment and eventual cure for AT and supports a national AT clinic in Nottingham, England. The Society also endeavors to raise awareness of A-T in both the medical community and the general population through brochures such as 'What Is A-T?' and 'Ataxia-Telangiectasia: A Guide for Teachers.' The Society keeps its members informed of advancements in research through a regular newsletter, 'A-T Society News,' and various publications including 'Ataxia-Telangiectasia: A Guide For Parents,' 'Ataxia-Telangiectasia: A Guide to Therapies,' and 'Ataxia-Telangiectasia: A Guide to Pre-Natal Diagnosis and the Genetic Aspects of A-T.'

- **Canadian Immunodeficiencies Patient Organization**

Address: Canadian Immunodeficiencies Patient Organization 1695 Pickmere Court, Mississauga, Ontario, L4X 1Z3, Canada

Telephone: (905) 206-0075

Fax: (905) 629-6945

Email: emctimo@concentric.net

Web Site: <http://www.concentric.net/~Emctim>

Background: The Canadian Immunodeficiencies Patient Organization (CIPO) is a national not-for-profit organization consisting of individuals with primary immunodeficiencies (PIDs) and their families. Established in 1997 and currently consisting of approximately 500 members and 10 chapters, the CIPO is dedicated to uniting the experience, resources, and expertise of its members to achieve nationwide improvement in the care and treatment of individuals with PIDs. Primary immunodeficiencies are inherited disorders characterized by irregularities in the cell development and/or cell maturation process of the immune system. Affected individuals may be abnormally prone to certain infections, be susceptible to particular forms of cancer, and/or have additional characteristic symptoms and findings. According to the World Health Organization, there are approximately 70 primary immunodeficiencies including x-linked agammaglobulinemia, common variable immunodeficiency, selective IgA deficiency, and severe combined immunodeficiency (SCID). The Canadian Immunodeficiencies Patient Organization is committed to establishing a central database of affected individuals in Canada; creating

an electronic library that may be accessed by individuals with PIDs, their families, and the general public; and supporting and encouraging the development of support groups in regional areas as well as via the World Wide Web on the Internet. The organization is also dedicated to creating a directory of physicians currently diagnosing and treating individuals with PIDs in Canada; providing networking opportunities to affected individuals and families; and educating the medical community, affected families, and the general public about primary immunodeficiencies. The CIPO's educational materials include brochures and a regular newsletter. In addition, the organization has a web site on the Internet that provides understandable information on PIDs, a guestbook for online visitors, and dynamic linkage to additional sources of information and support on the Internet.

- **Immune Deficiency Foundation**

Address: Immune Deficiency Foundation 25 West Chesapeake Avenue,  
Suite 206, Towson, MD 21204

Telephone: (410) 321-6647 Toll-free: (800) 296-4433

Fax: (410) 321-9165

Email: [idf@clark.net](mailto:idf@clark.net)

Web Site: <http://www.primaryimmune.or>

Background: The Immune Deficiency Foundation is a national not-for-profit voluntary health organization that was founded in 1980 by a group of parents with children affected by primary immune deficiency diseases. The Foundation has concentrated on creating a national focus for these disorders by supporting research, physician training, and patient and family education. The objectives of the Foundation are to promote and support scientific research into the causes, prevention, treatment, and cure of primary immune deficiency diseases; to promote training in medical research and clinical treatment; to gather, coordinate, and disseminate information concerning research and treatment of these disorders; to conduct education campaigns to increase public awareness; and to establish support systems for affected individuals and families throughout the United States. The Foundation produces a variety of educational materials including general information booklets, illustrated booklets for children, and a slide set entitled 'Our Immune System.'

- **International Patient Organization for Primary Immunodeficiencies**

Address: International Patient Organization for Primary  
Immunodeficiencies Web Site on the Internet,



Telephone: (414) 272-6071 Toll-free: (800) 822-2762

Web Site: <http://ipopi.org>

Background: The International Patient Organization for Primary Immunodeficiencies (IPOPI) is an international organization whose members are national patient organizations for the Primary Immunodeficiencies (PIDs). The organization was formed to benefit and serve its members and individuals with Primary Immunodeficiencies. Its purpose is to unite the experience, expertise, resources, and influence of its members in order to achieve worldwide improvement in the care and treatment of individuals with Primary Immunodeficiency Disorders. IPOPI strives to be responsive on an international level to the issues of greatest concern to its members. These issues include blood product safety, improving patient diagnosis, gene therapy, immunoglobulin therapy, patient organization development, patient and professional education, and prospects from mapping the human genome. The IPOPI's web site includes a listing of all IPOPI Member Organizations and International Support Groups, patient and family information on various Primary Immunodeficiency Disorders, the IPOPI current newsletter and archives, and an international listing of clinical services. The site also provides access to the IPOPI's ListServ and Fax Service, an interactive area consisting of a chat line and discussion forums, clinical updates, a patient family handbook for the Primary Immunodeficiency Disorders, other educational materials, the ability to search the entire web site by specific keywords, and an area containing dynamic linkage to related immunological web sites.

- **Jeffrey Modell Foundation**

Address: Jeffrey Modell Foundation 43 West 47th Street, 5th Floor, New York, NY 10036

Telephone: (212) 575-1122 Toll-free: (800) 533-3844

Fax: (212) 764- 4180

Email: [info@jmfworld.com](mailto:info@jmfworld.com)

Web Site: <http://www.jmfworld.com>

Background: The Jeffrey Modell Foundation (JMF) is a national not-for-profit research foundation dedicated to helping individuals and family members affected by primary immune deficiency disorders. The Foundation is active in four main areas: research, physician and patient education, patient support, and public awareness of primary immune deficiency. The Foundation provides funding of research fellowships and laboratory facilities; sponsors physician symposia in the United States,

Canada, and Europe as well as grand rounds, seminars, and other educational activities for physicians; offers publications for both the lay and medical communities; and provides affected individuals with access to leading medical centers with departments of clinical immunology. The JMF also sponsors K.I.D.'s (Kids with Immunodeficiency) Days for affected children and their families; has insurance reimbursement workshops for affected individuals and family members; is engaged in ongoing education campaigns to promote awareness of primary immune deficiency (PID) in the general public; conducts advocacy on behalf of affected individuals by lobbying the U.S. Congress; and is committed to ongoing biomedical research into primary immune deficiency at the National Institutes of Health. The JMF also publishes a regular newsletter for affected individuals and family members, physicians, and researchers; offers general materials on the primary immune deficiency disorders as well as materials on specific PID disorders for lay and medical audiences; and has a 24-hour JMF Hotline at (800) Jeff-844, which has assisted thousands of families throughout the United States. The JMF also has a web site on the Internet at <http://www.mssm.edu/peds/modell/>.

- **March of Dimes Birth Defects Foundation**

Address: March of Dimes Birth Defects Foundation 1275 Mamaroneck Avenue, White Plains, NY 10605

Telephone: (914) 428-7100 Toll-free: (888) 663-4637

Fax: (914) 997-4763

Email: [resourcecenter@modimes.org](mailto:resourcecenter@modimes.org)

Web Site: <http://www.modimes.org>

Background: The March of Dimes Birth Defects Foundation is a national not-for-profit organization that was established in 1938. The mission of the Foundation is to improve the health of babies by preventing birth defects and infant mortality. Through the Campaign for Healthier Babies, the March of Dimes funds programs of research, community services, education, and advocacy. Educational programs that seek to prevent birth defects are important to the Foundation and to that end it produces a wide variety of printed informational materials and videos. The March of Dimes public health educational materials provide information encouraging health-enhancing behaviors that lead to a healthy pregnancy and a healthy baby.

Relevant area(s) of interest: Down Syndrome, Fragile X Syndrome, Klinefelter Syndrome, McCune Albright Syndrome, Phenylketonuria

- **Primary Immunodeficiency Association (UK)**

Address: Primary Immunodeficiency Association (UK) Alliance House,  
12 Caxton Street, London, SW1H 0QS, United Kingdom

Telephone: 044 171 976 7640 Toll-free: (800) 296-4433

Fax: 044 171 976 7640

Email: [pimmune@dial.pipex.com](mailto:pimmune@dial.pipex.com)

Web Site: <http://www.pia.org.uk>

Background: The Primary Immunodeficiency Association (UK) is a voluntary not-for-profit organization in the United Kingdom dedicated to promoting awareness and early diagnosis of the various primary immunodeficiency disorders; ensuring that all affected individuals have access to the best possible treatment; providing information and support to individuals with primary immunodeficiencies, family members, and other caregivers; and encouraging and supporting original research. The primary immunodeficiencies are a group of rare genetic disorders characterized by irregularities in the cell development and/or cell maturation process of the immune system. Individuals with primary immunodeficiencies may be abnormally prone to certain bacterial, viral, fungal, and/or other infections, may experience repeated 'opportunistic' infections, and may be unusually susceptible to certain forms of cancer. ('Opportunistic' infections are infections caused by microorganisms that usually do not cause disease in individuals with fully functioning immune systems or widespread [systemic] overwhelming disease by microorganisms that typically cause only localized, mild infections.) The Primary Immunodeficiency Association (UK) was established in 1990 and currently consists of 12 chapters and approximately 1,500 members. The Association engages in patient advocacy; puts members in touch with one another through regional contacts and the organization's national database; and offers four or five 'regional days' every year at different locations where members may network and hear presentations by immunologists. The Primary Immunodeficiency Association also provides a telephone help service during and after regular office hours; provides information and assistance concerning benefits; has a youth service for young adults and adolescents with primary immunodeficiencies; and conducts annual medical student workshops to encourage specialization in immunology. The Association's educational materials include information packets for lay people and professionals, leaflets that provide understandable information on specific primary immunodeficiency disorders and other related topics, leaflets for teachers, booklets, and a quarterly newsletter entitled 'INSIGHT.' The

Primary Immunodeficiency Association (UK) also has a web site on the Internet at <http://www.pia.org.uk>.

## **Finding More Associations**

There are a number of directories that list additional medical associations that you may find useful. While not all of these directories will provide different information than what is listed above, by consulting all of them, you will have nearly exhausted all sources for parent associations.

### **The National Health Information Center (NHIC)**

The National Health Information Center (NHIC) offers a free referral service to help people find organizations that provide information about primary immunodeficiency. For more information, see the NHIC's Web site at <http://www.health.gov/NHIC/> or contact an information specialist by calling 1-800-336-4797.

### **DIRLINE**

A comprehensive source of information on associations is the DIRLINE database maintained by the National Library of Medicine. The database comprises some 10,000 records of organizations, research centers, and government institutes and associations which primarily focus on health and biomedicine. DIRLINE is available via the Internet at the following Web site: <http://dirline.nlm.nih.gov>. Simply type in "primary immunodeficiency" (or a synonym) or the name of a topic, and the site will list information contained in the database on all relevant organizations.

### **The Combined Health Information Database**

Another comprehensive source of information on healthcare associations is the Combined Health Information Database. Using the "Detailed Search" option, you will need to limit your search to "Organizations" and "primary immunodeficiency". Type the following hyperlink into your Web browser: <http://chid.nih.gov/detail/detail.html>. To find associations, use the drop boxes at the bottom of the search page where "You may refine your search by." For publication date, select "All Years." Then, select your preferred

language and the format option “Organization Resource Sheet.” By making these selections and typing in “primary immunodeficiency” (or synonyms) into the “For these words:” box, you will only receive results on organizations dealing with primary immunodeficiency. You should check back periodically with this database since it is updated every 3 months.

### **The National Organization for Rare Disorders, Inc.**

The National Organization for Rare Disorders, Inc. has prepared a Web site that provides, at no charge, lists of associations organized by specific medical conditions. You can access this database at the following Web site: **<http://www.rarediseases.org/cgi-bin/nord/searchpage>**. Select the option called “Organizational Database (ODB)” and type “primary immunodeficiency” (or a synonym) in the search box.

### **Online Support Groups**

In addition to support groups, commercial Internet service providers offer forums and chat rooms to discuss different illnesses and conditions. WebMD®, for example, offers such a service at their Web site: **<http://boards.webmd.com/roundtable>**. These online communities can help you connect with a network of people whose concerns are similar to yours. Online support groups are places where people can talk informally. If you read about a novel approach, consult with your child’s doctor or other healthcare providers, as the treatments or discoveries you hear about may not be scientifically proven to be safe and effective. The following Internet sites may be of particular interest:

- **Primary Immunodeficiency Association**  
<http://www.immunedisease.com/patient/patlinks.cfm>
- **Med Help**  
<http://www.medhelp.org/HealthTopics/Granuloma.html>
- **Primary Immunodeficiency Association**  
<http://www.pidsnz.co.nz/links.htm>

## Finding Doctors

All parents must go through the process of selecting a physician for their children with primary immunodeficiency. While this process will vary, the Agency for Healthcare Research and Quality makes a number of suggestions, including the following:<sup>10</sup>

- If your child is in a managed care plan, check the plan's list of doctors first.
- Ask doctors or other health professionals who work with doctors, such as hospital nurses, for referrals.
- Call a hospital's doctor referral service, but keep in mind that these services usually refer you to doctors on staff at that particular hospital. The services do not have information on the quality of care that these doctors provide.
- Some local medical societies offer lists of member doctors. Again, these lists do not have information on the quality of care that these doctors provide.

Additional steps you can take to locate doctors include the following:

- Check with the associations listed earlier in this chapter.
- Information on doctors in some states is available on the Internet at **<http://www.docboard.org>**. This Web site is run by "Administrators in Medicine," a group of state medical board directors.
- The American Board of Medical Specialties can tell you if your child's doctor is board certified. "Certified" means that the doctor has completed a training program in a specialty and has passed an exam, or "board," to assess his or her knowledge, skills, and experience to provide quality patient care in that specialty. Primary care doctors may also be certified as specialists. The ABMS Web site is located at **<http://www.abms.org/newsearch.asp>**.<sup>11</sup> You can also contact the ABMS by phone at 1-866-ASK-ABMS.
- You can call the American Medical Association (AMA) at 800-665-2882 for information on training, specialties, and board certification for many licensed doctors in the United States. This information also can be found in "Physician Select" at the AMA's Web site: **<http://www.ama-assn.org/aps/amahg.htm>**.

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<sup>10</sup> This section has been adapted from the AHRQ: **[www.ahrq.gov/consumer/qntascii/qntdr.htm](http://www.ahrq.gov/consumer/qntascii/qntdr.htm)**.

<sup>11</sup> While board certification is a good measure of a doctor's knowledge, it is possible to receive quality care from doctors who are not board certified.

If the previous sources did not meet your needs, you may want to log on to the Web site of the National Organization for Rare Disorders (NORD) at <http://www.rarediseases.org/>. NORD maintains a database of doctors with expertise in various rare medical conditions. The Metabolic Information Network (MIN), 800-945-2188, also maintains a database of physicians with expertise in various metabolic diseases.

## Finding a Pediatrician

The American Academy of Pediatrics (AAP) mission is “to attain optimal physical, mental, and social health and well-being for all infants, children, adolescents, and young adults.”<sup>12</sup> The AAP maintains an online pediatrician referral service which is available to the public and free of charge. This service allows you to search the AAP’s database of its 55,000 members which include pediatricians, pediatric medical subspecialists, and pediatric surgical specialists practicing in the U.S., Canada, and internationally.

To access the pediatrician referral service, log on to <http://www.aap.org/referral/> and read the terms and conditions of use. Once you accept the terms, you can search for pediatricians by name, city, state, or country. All AAP members listed in the referral service database are board-certified pediatricians.

## Selecting Your Doctor<sup>13</sup>

When you have compiled a list of prospective doctors, call each of their offices. First, ask if the doctor accepts your child’s health insurance plan and if he or she is taking new patients. If the doctor is not covered by your child’s plan, ask yourself if you are prepared to pay the extra costs. The next step is to schedule a visit with your first choice. During the first visit you will have the opportunity to evaluate your child’s doctor and to find out if your child feels comfortable with him or her.

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<sup>12</sup> The American Academy of Pediatrics: <http://www.aap.org/>.

<sup>13</sup> This section has been adapted from the AHRQ: [www.ahrq.gov/consumer/qntascii/qntdr.htm](http://www.ahrq.gov/consumer/qntascii/qntdr.htm).

## Working with Your Child's Doctor<sup>14</sup>

Research has shown that parents who have good relationships with their children's doctors tend to be more satisfied with their children's care. Here are some tips to help you and your child's doctor become partners:

- You know important things about your child's symptoms and health history. Tell the doctor what you think he or she needs to know.
- Always bring any medications your child is currently taking with you to the appointment, or you can bring a list of your child's medications including dosage and frequency information. Talk about any allergies or reactions your child has had to medications.
- Tell your doctor about any natural or alternative medicines your child is taking.
- Bring other medical information, such as x-ray films, test results, and medical records.
- Ask questions. If you don't, the doctor will assume that you understood everything that was said.
- Write down your questions before the doctor's visit. List the most important ones first to make sure that they are addressed.
- Ask the doctor to draw pictures if you think that this will help you and your child understand.
- Take notes. Some doctors do not mind if you bring a tape recorder to help you remember things, but always ask first.
- Take information home. Ask for written instructions. Your child's doctor may also have brochures and audio and videotapes on primary immunodeficiency.

By following these steps, you will enhance the relationship you and your child have with the physician.

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<sup>14</sup> This section has been adapted from the AHRQ:  
[www.ahrq.gov/consumer/qntascii/qntdr.htm](http://www.ahrq.gov/consumer/qntascii/qntdr.htm).



## Broader Health-Related Resources

In addition to the references above, the NIH has set up guidance Web sites that can help parents find healthcare professionals. These include:<sup>15</sup>

- Caregivers:  
<http://www.nlm.nih.gov/medlineplus/caregivers.html>
- Choosing a Doctor or Healthcare Service:  
<http://www.nlm.nih.gov/medlineplus/choosingadoctororhealthcareservice.html>
- Hospitals and Health Facilities:  
<http://www.nlm.nih.gov/medlineplus/healthfacilities.html>

## Vocabulary Builder

The following vocabulary builder provides definitions of words used in this chapter that have not been defined in previous chapters:

**Anaphylaxis:** An acute hypersensitivity reaction due to exposure to a previously encountered antigen. The reaction may include rapidly progressing urticaria, respiratory distress, vascular collapse, systemic shock, and death. [NIH]

**Lesion:** Any pathological or traumatic discontinuity of tissue or loss of function of a part. [EU]

**Microorganism:** A microscopic organism; those of medical interest include bacteria, viruses, fungi and protozoa. [EU]

**Nystagmus:** An involuntary, rapid, rhythmic movement of the eyeball, which may be horizontal, vertical, rotatory, or mixed, i.e., of two varieties. [EU]

**Predisposition:** A latent susceptibility to disease which may be activated under certain conditions, as by stress. [EU]

**Rhinitis:** Inflammation of the mucous membrane of the nose. [EU]

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<sup>15</sup> You can access this information at:

<http://www.nlm.nih.gov/medlineplus/healthsystem.html>.



## CHAPTER 3. CLINICAL TRIALS AND PRIMARY IMMUNODEFICIENCY

### Overview

Very few medical conditions have a single treatment. The basic treatment guidelines that your child's physician has discussed with you, or those that you have found using the techniques discussed in Chapter 1, may provide you with all that you will require. For some patients, current treatments can be enhanced with new or innovative techniques currently under investigation. In this chapter, we will describe how clinical trials work and show you how to keep informed of trials concerning primary immunodeficiency.

### What Is a Clinical Trial?<sup>16</sup>

Clinical trials involve the participation of people in medical research. Most medical research begins with studies in test tubes and on animals. Treatments that show promise in these early studies may then be tried with people. The only sure way to find out whether a new treatment is safe, effective, and better than other treatments for primary immunodeficiency is to try it on patients in a clinical trial.

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<sup>16</sup> The discussion in this chapter has been adapted from the NIH and the NEI: [www.nei.nih.gov/netrials/ctivr.htm](http://www.nei.nih.gov/netrials/ctivr.htm).

## What Kinds of Clinical Trials Are There?

Clinical trials are carried out in three phases:

- **Phase I.** Researchers first conduct Phase I trials with small numbers of patients and healthy volunteers. If the new treatment is a medication, researchers also try to determine how much of it can be given safely.
- **Phase II.** Researchers conduct Phase II trials in small numbers of patients to find out the effect of a new treatment on primary immunodeficiency.
- **Phase III.** Finally, researchers conduct Phase III trials to find out how new treatments for primary immunodeficiency compare with standard treatments already being used. Phase III trials also help to determine if new treatments have any side effects. These trials--which may involve hundreds, perhaps thousands, of people--can also compare new treatments with no treatment.

## How Is a Clinical Trial Conducted?

Various organizations support clinical trials at medical centers, hospitals, universities, and doctors' offices across the United States. The "principal investigator" is the researcher in charge of the study at each facility participating in the clinical trial. Most clinical trial researchers are medical doctors, academic researchers, and specialists. The "clinic coordinator" knows all about how the study works and makes all the arrangements for your child's visits.

All doctors and researchers who take part in the study on primary immunodeficiency carefully follow a detailed treatment plan called a protocol. This plan fully explains how the doctors will treat your child in the study. The "protocol" ensures that all patients are treated in the same way, no matter where they receive care.

Clinical trials are controlled. This means that researchers compare the effects of the new treatment with those of the standard treatment. In some cases, when no standard treatment exists, the new treatment is compared with no treatment. Patients who receive the new treatment are in the treatment group. Patients who receive a standard treatment or no treatment are in the "control" group. In some clinical trials, patients in the treatment group get a new medication while those in the control group get a placebo. A placebo is a harmless substance, a "dummy" pill, that has no effect on primary immunodeficiency. In other clinical trials, where a new surgery or device (not a medicine) is being tested, patients in the control group may receive a

“sham treatment.” This treatment, like a placebo, has no effect on primary immunodeficiency and will not harm your child.

Researchers assign patients “randomly” to the treatment or control group. This is like flipping a coin to decide which patients are in each group. If you choose to have your child participate in a clinical trial, you will not know which group he or she will be appointed to. The chance of any patient getting the new treatment is about 50 percent. You cannot request that your child receive the new treatment instead of the placebo or “sham” treatment. Often, you will not know until the study is over whether your child has been in the treatment group or the control group. This is called a “masked” study. In some trials, neither doctors nor patients know who is getting which treatment. This is called a “double masked” study. These types of trials help to ensure that the perceptions of the participants or doctors will not affect the study results.

### **Natural History Studies**

Unlike clinical trials in which patient volunteers may receive new treatments, natural history studies provide important information to researchers on how primary immunodeficiency develops over time. A natural history study follows patient volunteers to see how factors such as age, sex, race, or family history might make some people more or less at risk for primary immunodeficiency. A natural history study may also tell researchers if diet, lifestyle, or occupation affects how a medical condition develops and progresses. Results from these studies provide information that helps answer questions such as: How fast will a medical condition usually progress? How bad will the condition become? Will treatment be needed?

### **What Is Expected of Your Child in a Clinical Trial?**

Not everyone can take part in a clinical trial for a specific medical condition. Each study enrolls patients with certain features or eligibility criteria. These criteria may include the type and stage of the condition, as well as, the age and previous treatment history of the patient. You or your child’s doctor can contact the sponsoring organization to find out more about specific clinical trials and their eligibility criteria. If you would like your child to participate in a clinical trial, your child’s doctor must contact one of the trial’s investigators and provide details about his or her diagnosis and medical history.

When participating in a clinical trial, your child may be required to have a number of medical tests. Your child may also need to take medications and/or undergo surgery. Depending upon the treatment and the examination procedure, your child may be required to receive inpatient hospital care. He or she may have to return to the medical facility for follow-up examinations. These exams help find out how well the treatment is working. Follow-up studies can take months or years. However, the success of the clinical trial often depends on learning what happens to patients over a long period of time. Only patients who continue to return for follow-up examinations can provide this important long-term information.

## Recent Trials on Primary Immunodeficiency

The National Institutes of Health and other organizations sponsor trials on various medical conditions. Because funding for research goes to the medical areas that show promising research opportunities, it is not possible for the NIH or others to sponsor clinical trials for every medical condition at all times. The following lists recent trials dedicated to primary immunodeficiency.<sup>17</sup> If the trial listed by the NIH is still recruiting, your child may be eligible. If it is no longer recruiting or has been completed, then you can contact the sponsors to learn more about the study and, if published, the results. Further information on the trial is available at the Web site indicated. Please note that some trials may no longer be recruiting patients or are otherwise closed. Before contacting sponsors of a clinical trial, consult with your child's physician who can help you determine if your child might benefit from participation.

- **Genetic Basis of Primary Immunodeficiencies**

Condition(s): Immunologic Deficiency Syndrome

Study Status: This study is currently recruiting patients.

Sponsor(s): National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

Purpose - Excerpt: The purpose of this study is to evaluate patients with primary immunodeficiency disorders to identify patients with mutations of the genes for the following proteins: Jak3, STAT1, STAT4, interleukin-7, interleukin-7 receptor, interleukin-12 receptor subunits, and others.

Patients will undergo screening history, physical examination, and clinical laboratory evaluation at referring institutions and tissue samples, or cell lines will be sent to the NIH. We will establish cell lines if

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<sup>17</sup> These are listed at [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov).

necessary, prepare DNA and RNA for molecular genetic analysis and study cytokine signal transduction in patient cell lines.

Study Type: Observational

Contact(s): Maryland; National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), 9000 Rockville Pike Bethesda, Maryland, 20892, United States; Recruiting; Patient Recruitment and Public Liaison Office 1-800-411-1222 prpl@mail.cc.nih.gov; TTY 1-866-411-1010

Web Site:

<http://clinicaltrials.gov/ct/gui/show/NCT00001788;jsessionid=14C554A2C411E1E2F2924395B253C6A6>

- **Molecular and Clinical Studies of Primary Immunodeficiency diseases**

Condition(s): Immunologic Deficiency Syndrome

Study Status: This study is currently recruiting patients.

Sponsor(s): National Human Genome Research Institute (NHGRI)

Purpose - Excerpt: This study will try to identify mutations in the genes responsible for primary immunodeficiency disorders (inherited diseases of the immune system) and evaluate the course of these diseases in patients over time to learn more about the medical problems they cause. The immune system is composed of various cells (e.g., T and B cells and phagocytes) and other substances (complement system) that protect the body from infections and cancer. Abnormalities in the gene(s) responsible for the function of these components can lead to serious infections and other immune problems. Patients with Wiskott-Aldrich syndrome, adenosine deaminase (ADA) deficiency, Janus Associated Kinase 3 (JAK3) deficiency, common variable immunodeficiency (CVID) and other immunodeficiencies may be eligible for this study. Participants will undergo a medical and family history, physical examination, and additional procedures and tests that may include the following: 1. Blood tests for: routine laboratory studies (i.e. cell counts, enzyme levels, electrolytes, etc.); HIV testing; immune response to various substances; genetic testing; and establishment of cell lines to maintain a supply of cells for continued study 2. Urine and saliva tests for biochemical studies 3. Skin tests to assess response to antigens such as the viruses and bacteria responsible for tetanus, candida, tuberculosis, diphtheria, chicken pox, and other diseases. 4. Skin and lymph node biopsies for tissue and DNA studies 5. Chest X-ray, CT scans, or both to look for cancer or various infections. 6. Pulmonary function test to assess lung capacity and a breath test to test for H. pylori infection. 7. Dental, skin and eye examinations. 8. Treatment with intravenous immunoglobulins or antibodies to prevent infections. 9. Apheresis for collecting white

blood cells to study cell function. In this procedure, whole blood is collected through a needle placed in an arm vein. The blood circulates through a machine that separates it into its components. The white cells are then removed, and the red cells, platelets and plasma are returned to the body, either through the same needle or through a second needle placed in the other arm. 10. Bone marrow sampling to study the disease. A small amount of marrow from the hipbone is drawn (aspirated) through a needle. The procedure can be done under local anesthesia or light sedation. 11. Placental and umbilical cord blood studies, if cord blood is available, to study stem cells (cells that form blood cells). Information gained from this study may provide a better understanding of primary immunodeficiencies, leading to better diagnosis and treatment. In addition, study participants may receive medical and genetic counseling and may be found eligible for other NIH studies on these diseases.

Study Type: Observational

Contact(s): Maryland; National Human Genome Research Institute (NHGRI), 9000 Rockville Pike Bethesda, Maryland, 20892, United States; Recruiting; Patient Recruitment and Public Liaison Office 1-800-411-1222 prpl@mail.cc.nih.gov; TTY 1-866-411-1010

Web Site:

<http://clinicaltrials.gov/ct/gui/show/NCT00006319;jsessionid=14C554A2C411E1E2F2924395B253C6A6>

- **Pilot Study of Allogeneic Bone Marrow Transplantation Plus Cyclosporine and Mycophenolate Mofetil to Induce Mixed Hematopoietic Chimerism in Patients With Primary T-Cell Immunodeficiency Disorders**

Condition(s): Purine-Pyrimidine Metabolism, Inborn Errors; Wiskott-Aldrich Syndrome; Bare Lymphocyte Syndrome; Lymphopenia; Job's Syndrome; DiGeorge Syndrome; Omenn syndrome; X-linked hyper IgM syndrome; Severe Combined Immunodeficiency; Immunologic Deficiency Syndromes

Study Status: This study is currently recruiting patients.

Sponsor(s): Fred Hutchinson Cancer Research Center

Purpose - Excerpt: Objectives: I. Determine the safety of cyclosporine and mycophenolate mofetil as a non-ablative conditioning and post-transplantation immunosuppression regimen in patients with primary T-cell immunodeficiency disorders who undergo HLA-matched related or unrelated bone marrow transplantation to induce mixed hematopoietic chimerism (establishment of 1-95% donor CD3+ cells). II. Determine the



kinetics of immune reconstitution of lymphoid cell subsets, T-cell function, and B-cell function after allogeneic bone marrow transplantation in this patient population.

Phase(s): Phase I

Study Type: Interventional

Contact(s): Washington; Fred Hutchinson Cancer Research Center, Seattle, Washington, 98109, United States; Recruiting; Ann Woolfrey 206-667-4453. Study chairs or principal investigators: Ann Woolfrey, Study Chair; Fred Hutchinson Cancer Research Center

Web Site:

<http://clinicaltrials.gov/ct/gui/show/NCT00008450;jsessionid=14C554A2C411E1E2F2924395B253C6A6>

- **Study of Genetic and Molecular Defects in Primary Immunodeficiency Disorders**

Condition(s): X-linked agammaglobulinemia; X-linked hyper IgM syndrome; Wiskott-Aldrich Syndrome; Leukocyte Adhesion Deficiency Syndrome

Study Status: This study is currently recruiting patients.

Sponsor(s): National Institute of Child Health and Human Development (NICHD); University of Washington

Purpose - Excerpt: Objectives: I. Identify the molecular defects responsible for primary immunodeficiency disorders. II. Explore the mutations within each syndrome to better understand the genetics of these disorders. III. Study the function of the Wiskott-Aldrich syndrome proteins (WASP). IV. Design methods to identify carriers and for prenatal diagnosis. V. Explore new avenues for therapy.

Study Type: Observational

Contact(s): see Web site below

Web Site:

<http://clinicaltrials.gov/ct/gui/show/NCT00004341;jsessionid=14C554A2C411E1E2F2924395B253C6A6>

## **Benefits and Risks<sup>18</sup>**

### **What Are the Benefits of Participating in a Clinical Trial?**

If you are considering a clinical trial, it is important to realize that your child's participation can bring many benefits:

- A new treatment could be more effective than the current treatment for primary immunodeficiency. Although only half of the participants in a clinical trial receive the experimental treatment, if the new treatment is proved to be more effective and safer than the current treatment, then those patients who did not receive the new treatment during the clinical trial may be among the first to benefit from it when the study is over.
- If the treatment is effective, then it may improve your child's health.
- Clinical trial patients receive the highest quality of medical care. Experts watch them closely during the study and may continue to follow them after the study is over.
- People who take part in trials contribute to scientific discoveries that may help others with primary immunodeficiency. In cases where certain medical conditions run in families, your child's participation may lead to better care or prevention for you and other family members.

### **The Informed Consent**

Once you agree to have your child take part in a clinical trial, you will be asked to sign an "informed consent." This document explains a clinical trial's risks and benefits, the researcher's expectations of you and your child, and your child's rights as a patient.

### **What Are the Risks?**

Clinical trials may involve risks as well as benefits. Whether or not a new treatment will work cannot be known ahead of time. There is always a chance that a new treatment may not work better than a standard treatment. There is also the possibility that it may be harmful. The treatment your child

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<sup>18</sup> This section has been adapted from ClinicalTrials.gov, a service of the National Institutes of Health:  
[http://www.clinicaltrials.gov/ct/gui/c/a1r/info/whatis?JServSessionIdzone\\_ct=9jmun6f291](http://www.clinicaltrials.gov/ct/gui/c/a1r/info/whatis?JServSessionIdzone_ct=9jmun6f291).

receives may cause side effects that are serious enough to require medical attention.

### **How Is Your Child's Safety Protected?**

Clinical trials can raise fears of the unknown. Understanding the safeguards that protect your child can ease some of these fears. Before a clinical trial begins, researchers must get approval from their hospital's Institutional Review Board (IRB), an advisory group that makes sure a clinical trial is designed to protect your child's safety. During a clinical trial, doctors will closely watch your child to see if the treatment is working and if he or she is experiencing any side effects. All the results are carefully recorded and reviewed. In many cases, experts from the Data and Safety Monitoring Committee carefully monitor each clinical trial and can recommend that a study be stopped at any time. Your child will only be asked to participate in a clinical trial as a volunteer with your informed consent.

### **What Are Your Child's Rights in a Clinical Trial?**

If your child is eligible for a clinical trial, you will be given information to help you decide whether or not you want him or her to participate. You and your child have the right to:

- Information on all known risks and benefits of the treatments in the study.
- Know how the researchers plan to carry out the study, for how long, and where.
- Know what is expected of your child.
- Know any costs involved for you or your child's insurance provider.
- Know before any of your child's medical or personal information is shared with other researchers involved in the clinical trial.
- Talk openly with doctors and ask any questions.

After your child joins a clinical trial, you and your child have the right to:

- Leave the study at any time. Participation is strictly voluntary.
- Receive any new information about the new treatment.
- Continue to ask questions and get answers.
- Maintain your child's privacy. Your child's name will not appear in any reports based on the study.

- Know whether your child participated in the treatment group or the control group (once the study has been completed).

### **What about Costs?**

In some clinical trials, the research facility pays for treatment costs and other associated expenses. You or your child's insurance provider may have to pay for costs that are considered standard care. These things may include inpatient hospital care, laboratory and other tests, and medical procedures. You also may need to pay for travel between your home and the clinic. You should find out about costs before committing your child to participation in the trial. If your child has health insurance, find out exactly what it will cover. If your child does not have health insurance, or if your child's insurance policy will not cover care, talk to the clinic staff about other options for covering the costs.

### **What Questions Should You Ask before Your Child Participates in a Clinical Trial?**

Questions you should ask when deciding whether or not to enroll your child in a clinical trial include the following:

- What is the purpose of the clinical trial?
- What are the standard treatments for primary immunodeficiency? Why do researchers think the new treatment may be better? What is likely to happen to my child with or without the new treatment?
- What tests and treatments will my child need? Will my child need surgery? Medication? Hospitalization?
- How long will the treatment last? How often will my child have to come back for follow-up exams?
- What are the treatment's possible benefits to my child's condition? What are the short- and long-term risks? What are the possible side effects?
- Will the treatment be uncomfortable? Will it make my child sick? If so, for how long?
- How will my child's health be monitored?
- Where will my child need to go for the clinical trial?
- How much will it cost to participate in the study? What costs are covered by the study? How much will my child's health insurance cover?
- Who will be in charge of my child's care?

- Will taking part in the study affect my child's daily life?
- How does my child feel about taking part in a clinical trial? Will other family members benefit from my child's contributions to new medical knowledge?

## Keeping Current on Clinical Trials

Various government agencies maintain databases on trials. The U.S. National Institutes of Health, through the National Library of Medicine, has developed ClinicalTrials.gov to provide the public and physicians with current information about clinical research across the broadest number of medical conditions.

The site was launched in February 2000 and currently contains approximately 5,700 clinical studies in over 59,000 locations worldwide, with most studies being conducted in the United States. ClinicalTrials.gov receives about 2 million hits per month and hosts approximately 5,400 visitors daily. To access this database, simply go to their Web site ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) and search by "primary immunodeficiency" (or synonyms).

While ClinicalTrials.gov is the most comprehensive listing of NIH-supported clinical trials available, not all trials are in the database. The database is updated regularly, so clinical trials are continually being added. The following is a list of specialty databases affiliated with the National Institutes of Health that offer additional information on trials:

- For clinical studies at the Warren Grant Magnuson Clinical Center located in Bethesda, Maryland, visit their Web site:  
<http://clinicalstudies.info.nih.gov/>
- For clinical studies conducted at the Bayview Campus in Baltimore, Maryland, visit their Web site:  
<http://www.jhbmc.jhu.edu/studies/index.html>

## General References

The following references describe clinical trials and experimental medical research. They have been selected to ensure that they are likely to be available from your local or online bookseller or university medical library. These references are usually written for healthcare professionals, so you may consider consulting with a librarian or bookseller who might recommend a

particular reference. The following includes some of the most readily available references (sorted alphabetically by title; hyperlinks provide rankings, information and reviews at Amazon.com):

- **A Guide to Patient Recruitment : Today's Best Practices & Proven Strategies** by Diana L. Anderson; Paperback - 350 pages (2001), CenterWatch, Inc.; ISBN: 1930624115;  
<http://www.amazon.com/exec/obidos/ASIN/1930624115/icongroupinterna>
- **A Step-By-Step Guide to Clinical Trials** by Marilyn Mulay, R.N., M.S., OCN; Spiral-bound - 143 pages Spiral edition (2001), Jones & Bartlett Pub; ISBN: 0763715697;  
<http://www.amazon.com/exec/obidos/ASIN/0763715697/icongroupinterna>
- **The CenterWatch Directory of Drugs in Clinical Trials** by CenterWatch; Paperback - 656 pages (2000), CenterWatch, Inc.; ISBN: 0967302935;  
<http://www.amazon.com/exec/obidos/ASIN/0967302935/icongroupinterna>
- **The Complete Guide to Informed Consent in Clinical Trials** by Terry Hartnett (Editor); Paperback - 164 pages (2000), PharmSource Information Services, Inc.; ISBN: 0970153309;  
<http://www.amazon.com/exec/obidos/ASIN/0970153309/icongroupinterna>
- **Dictionary for Clinical Trials** by Simon Day; Paperback - 228 pages (1999), John Wiley & Sons; ISBN: 0471985961;  
<http://www.amazon.com/exec/obidos/ASIN/0471985961/icongroupinterna>
- **Extending Medicare Reimbursement in Clinical Trials** by Institute of Medicine Staff (Editor), et al; Paperback 1st edition (2000), National Academy Press; ISBN: 0309068886;  
<http://www.amazon.com/exec/obidos/ASIN/0309068886/icongroupinterna>
- **Handbook of Clinical Trials** by Marcus Flather (Editor); Paperback (2001), Remedica Pub Ltd; ISBN: 1901346293;  
<http://www.amazon.com/exec/obidos/ASIN/1901346293/icongroupinterna>

## Vocabulary Builder

The following vocabulary builder gives definitions of words used in this chapter that have not been defined in previous chapters:

**Abdominal:** Pertaining to the abdomen. [EU]

**Adenosine:** A nucleoside that is composed of adenine and d-ribose. Adenosine or adenosine derivatives play many important biological roles in addition to being components of DNA and RNA. Adenosine itself is a neurotransmitter. [NIH]

**Adjuvant:** A substance which aids another, such as an auxiliary remedy; in immunology, nonspecific stimulator (e.g., BCG vaccine) of the immune response. [EU]

**Agammaglobulinemia:** An immunologic deficiency state characterized by an extremely low level of generally all classes of gamma-globulin in the blood. [NIH]

**Anemia:** A reduction in the number of circulating erythrocytes or in the quantity of hemoglobin. [NIH]

**Anesthesia:** A state characterized by loss of feeling or sensation. This depression of nerve function is usually the result of pharmacologic action and is induced to allow performance of surgery or other painful procedures. [NIH]

**Antibiotic:** A chemical substance produced by a microorganism which has the capacity, in dilute solutions, to inhibit the growth of or to kill other microorganisms. Antibiotics that are sufficiently nontoxic to the host are used as chemotherapeutic agents in the treatment of infectious diseases of man, animals and plants. [EU]

**Antibody:** An immunoglobulin molecule that has a specific amino acid sequence by virtue of which it interacts only with the antigen that induced its synthesis in cells of the lymphoid series (especially plasma cells), or with antigen closely related to it. Antibodies are classified according to their mode of action as agglutinins, bacteriolysins, haemolysins, opsonins, precipitins, etc. [EU]

**Antifungal:** Destructive to fungi, or suppressing their reproduction or growth; effective against fungal infections. [EU]

**Antigen:** Any substance which is capable, under appropriate conditions, of inducing a specific immune response and of reacting with the products of that response, that is, with specific antibody or specifically sensitized T-lymphocytes, or both. Antigens may be soluble substances, such as toxins and foreign proteins, or particulate, such as bacteria and tissue cells; however, only the portion of the protein or polysaccharide molecule known as the antigenic determinant (q.v.) combines with antibody or a specific receptor on a lymphocyte. Abbreviated Ag. [EU]

**Antiviral:** Destroying viruses or suppressing their replication. [EU]

**Aplasia:** Lack of development of an organ or tissue, or of the cellular products from an organ or tissue. [EU]

**Arginine:** An essential amino acid that is physiologically active in the L-form. [NIH]

**Arteritis:** Inflammation of an artery. [NIH]

**Aspiration:** The act of inhaling. [EU]

**Asymptomatic:** Showing or causing no symptoms. [EU]

**Bacteria:** Unicellular prokaryotic microorganisms which generally possess rigid cell walls, multiply by cell division, and exhibit three principal forms: round or coccid, rodlike or bacillary, and spiral or spirochetal. [NIH]

**Beclomethasone:** An anti-inflammatory, synthetic glucocorticoid. It is used topically as an anti-inflammatory agent and in aerosol form for the treatment of asthma. [NIH]

**Biochemical:** Relating to biochemistry; characterized by, produced by, or involving chemical reactions in living organisms. [EU]

**Biopsy:** The removal and examination, usually microscopic, of tissue from the living body, performed to establish precise diagnosis. [EU]

**Candidiasis:** Infection with a fungus of the genus *Candida*. It is usually a superficial infection of the moist cutaneous areas of the body, and is generally caused by *C. albicans*; it most commonly involves the skin (dermatocandidiasis), oral mucous membranes (thrush, def. 1), respiratory tract (bronchocandidiasis), and vagina (vaginitis). Rarely there is a systemic infection or endocarditis. Called also moniliasis, candidosis, oidiomycosis, and formerly blastodendriosis. [EU]

**Cefuroxime:** Broad-spectrum cephalosporin antibiotic resistant to beta-lactamase. It has been proposed for infections with gram-negative and gram-positive organisms, gonorrhea, and haemophilus. [NIH]

**Chemotherapy:** The treatment of disease by means of chemicals that have a specific toxic effect upon the disease - producing microorganisms or that selectively destroy cancerous tissue. [EU]

**Clarithromycin:** A semisynthetic macrolide antibiotic derived from erythromycin that is active against a variety of microorganisms. It can inhibit protein synthesis in bacteria by reversibly binding to the 50S ribosomal subunits. This inhibits the translocation of aminoacyl transfer-RNA and prevents peptide chain elongation. [NIH]

**Cyclophosphamide:** Precursor of an alkylating nitrogen mustard antineoplastic and immunosuppressive agent that must be activated in the liver to form the active aldophosphamide. It is used in the treatment of lymphomas, leukemias, etc. Its side effect, alopecia, has been made use of in defleecing sheep. Cyclophosphamide may also cause sterility, birth defects, mutations, and cancer. [NIH]

**Cytokines:** Non-antibody proteins secreted by inflammatory leukocytes and some non-leukocytic cells, that act as intercellular mediators. They differ from classical hormones in that they are produced by a number of tissue or cell types rather than by specialized glands. They generally act locally in a paracrine or autocrine rather than endocrine manner. [NIH]



**Cytomegalovirus:** A genus of the family herpesviridae, subfamily betaherpesvirinae, infecting the salivary glands, liver, spleen, lungs, eyes, and other organs, in which they produce characteristically enlarged cells with intranuclear inclusions. Infection with Cytomegalovirus is also seen as an opportunistic infection in AIDS. [NIH]

**Decongestant:** An agent that reduces congestion or swelling. [EU]

**Diphtheria:** A localized infection of mucous membranes or skin caused by toxigenic strains of corynebacterium diphtheriae. It is characterized by the presence of a pseudomembrane at the site of infection. Diphtheria toxin, produced by C. diphtheriae, can cause myocarditis, polyneuritis, and other systemic toxic effects. [NIH]

**Electrolyte:** A substance that dissociates into ions when fused or in solution, and thus becomes capable of conducting electricity; an ionic solute. [EU]

**Enzyme:** A protein molecule that catalyses chemical reactions of other substances without itself being destroyed or altered upon completion of the reactions. Enzymes are classified according to the recommendations of the Nomenclature Committee of the International Union of Biochemistry. Each enzyme is assigned a recommended name and an Enzyme Commission (EC) number. They are divided into six main groups; oxidoreductases, transferases, hydrolases, lyases, isomerases, and ligases. [EU]

**Esophagitis:** Inflammation, acute or chronic, of the esophagus caused by bacteria, chemicals, or trauma. [NIH]

**Fatigue:** The state of weariness following a period of exertion, mental or physical, characterized by a decreased capacity for work and reduced efficiency to respond to stimuli. [NIH]

**Fluconazole:** Triazole antifungal agent that is used to treat oropharyngeal candidiasis and cryptococcal meningitis in AIDS. [NIH]

**Foscarnet:** An antiviral agent used in the treatment of cytomegalovirus retinitis. Foscarnet also shows activity against human herpesviruses and HIV. [NIH]

**Ganciclovir:** Acyclovir analog that is a potent inhibitor of the Herpesvirus family including cytomegalovirus. Ganciclovir is used to treat complications from AIDS-associated cytomegalovirus infections. [NIH]

**Gastrointestinal:** Pertaining to or communicating with the stomach and intestine, as a gastrointestinal fistula. [EU]

**Glucose:** D-glucose, a monosaccharide (hexose), C<sub>6</sub>H<sub>12</sub>O<sub>6</sub>, also known as dextrose (q.v.), found in certain foodstuffs, especially fruits, and in the normal blood of all animals. It is the end product of carbohydrate metabolism and is the chief source of energy for living organisms, its utilization being controlled by insulin. Excess glucose is converted to

glycogen and stored in the liver and muscles for use as needed and, beyond that, is converted to fat and stored as adipose tissue. Glucose appears in the urine in diabetes mellitus. [EU]

**Hypersensitivity:** A state of altered reactivity in which the body reacts with an exaggerated immune response to a foreign substance. Hypersensitivity reactions are classified as immediate or delayed, types I and IV, respectively, in the Gell and Coombs classification (q.v.) of immune responses. [EU]

**Immunity:** The condition of being immune; the protection against infectious disease conferred either by the immune response generated by immunization or previous infection or by other nonimmunologic factors (innate i.). [EU]

**Immunization:** The induction of immunity. [EU]

**Immunosuppressant:** An agent capable of suppressing immune responses. [EU]

**Immunotherapy:** Manipulation of the host's immune system in treatment of disease. It includes both active and passive immunization as well as immunosuppressive therapy to prevent graft rejection. [NIH]

**Infusion:** The therapeutic introduction of a fluid other than blood, as saline solution, solution, into a vein. [EU]

**Insulin:** A protein hormone secreted by beta cells of the pancreas. Insulin plays a major role in the regulation of glucose metabolism, generally promoting the cellular utilization of glucose. It is also an important regulator of protein and lipid metabolism. Insulin is used as a drug to control insulin-dependent diabetes mellitus. [NIH]

**Intestines:** The section of the alimentary canal from the stomach to the anus. It includes the large intestine and small intestine. [NIH]

**Intravenous:** Within a vein or veins. [EU]

**Kinetic:** Pertaining to or producing motion. [EU]

**Lupus:** A form of cutaneous tuberculosis. It is seen predominantly in women and typically involves the nasal, buccal, and conjunctival mucosa. [NIH]

**Lymphopenia:** Reduction in the number of lymphocytes. [NIH]

**Maxillary:** Pertaining to the maxilla : the irregularly shaped bone that with its fellow forms the upper jaw. [EU]

**Mobilization:** The process of making a fixed part or stored substance mobile, as by separating a part from surrounding structures to make it accessible for an operative procedure or by causing release into the circulation for body use of a substance stored in the body. [EU]

**Molecular:** Of, pertaining to, or composed of molecules : a very small mass of matter. [EU]

**Monocytes:** Large, phagocytic mononuclear leukocytes produced in the vertebrate bone marrow and released into the blood; contain a large, oval or somewhat indented nucleus surrounded by voluminous cytoplasm and numerous organelles. [NIH]

**Mycobacterium:** An organism of the genus *Mycobacterium*. [EU]

**Myocarditis:** Inflammation of the myocardium; inflammation of the muscular walls of the heart. [EU]

**Neutrophil:** Having an affinity for neutral dyes. [EU]

**Pancreas:** A mixed exocrine and endocrine gland situated transversely across the posterior abdominal wall in the epigastric and hypochondriac regions. The endocrine portion is comprised of the islets of Langerhans, while the exocrine portion is a compound acinar gland that secretes digestive enzymes. [NIH]

**Plasmapheresis:** Procedure whereby plasma is separated and extracted from anticoagulated whole blood and the red cells retransfused to the donor. Plasmapheresis is also employed for therapeutic use. [NIH]

**Prednisone:** A synthetic anti-inflammatory glucocorticoid derived from cortisone. It is biologically inert and converted to prednisolone in the liver. [NIH]

**Prenatal:** Existing or occurring before birth, with reference to the fetus. [EU]

**Progressive:** Advancing; going forward; going from bad to worse; increasing in scope or severity. [EU]

**Prophylaxis:** The prevention of disease; preventive treatment. [EU]

**Proteins:** Polymers of amino acids linked by peptide bonds. The specific sequence of amino acids determines the shape and function of the protein. [NIH]

**Pulmonary:** Pertaining to the lungs. [EU]

**Purpura:** Purplish or brownish red discoloration, easily visible through the epidermis, caused by hemorrhage into the tissues. [NIH]

**Quinolones:** Quinolines which are substituted in any position by one or more oxo groups. These compounds can have any degree of hydrogenation, any substituents, and fused ring systems. [NIH]

**Receptor:** 1. a molecular structure within a cell or on the surface characterized by (1) selective binding of a specific substance and (2) a specific physiologic effect that accompanies the binding, e.g., cell-surface receptors for peptide hormones, neurotransmitters, antigens, complement fragments, and immunoglobulins and cytoplasmic receptors for steroid hormones. 2. a sensory nerve terminal that responds to stimuli of various kinds. [EU]

**Recombinant:** 1. a cell or an individual with a new combination of genes not

found together in either parent; usually applied to linked genes. [EU]

**Reconstitution:** 1. a type of regeneration in which a new organ forms by the rearrangement of tissues rather than from new formation at an injured surface. 2. the restoration to original form of a substance previously altered for preservation and storage, as the restoration to a liquid state of blood serum or plasma that has been dried and stored. [EU]

**Refractory:** Not readily yielding to treatment. [EU]

**Remission:** A diminution or abatement of the symptoms of a disease; also the period during which such diminution occurs. [EU]

**Reperfusion:** Restoration of blood supply to tissue which is ischemic due to decrease in normal blood supply. The decrease may result from any source including atherosclerotic obstruction, narrowing of the artery, or surgical clamping. It is primarily a procedure for treating infarction or other ischemia, by enabling viable ischemic tissue to recover, thus limiting further necrosis. However, it is thought that reperfusion can itself further damage the ischemic tissue, causing reperfusion injury. [NIH]

**Rheumatoid:** Resembling rheumatism. [EU]

**Rifabutin:** A broad-spectrum antibiotic that is being used as prophylaxis against disseminated *Mycobacterium avium* complex infection in HIV-positive patients. [NIH]

**Saliva:** The clear, viscous fluid secreted by the salivary glands and mucous glands of the mouth. It contains mucins, water, organic salts, and ptylin. [NIH]

**Sinusitis:** Inflammation of a sinus. The condition may be purulent or nonpurulent, acute or chronic. Depending on the site of involvement it is known as ethmoid, frontal, maxillary, or sphenoid sinusitis. [EU]

**Sirolimus:** A macrolide compound obtained from *Streptomyces hygroscopicus* that acts by selectively blocking the transcriptional activation of cytokines thereby inhibiting cytokine production. It is bioactive only when bound to immunophilins. Sirolimus is a potent immunosuppressant and possesses both antifungal and antineoplastic properties. [NIH]

**Spectrum:** A charted band of wavelengths of electromagnetic vibrations obtained by refraction and diffraction. By extension, a measurable range of activity, such as the range of bacteria affected by an antibiotic (antibacterial s.) or the complete range of manifestations of a disease. [EU]

**Steroid:** A group name for lipids that contain a hydrogenated cyclopentanoperhydrophenanthrene ring system. Some of the substances included in this group are progesterone, adrenocortical hormones, the gonadal hormones, cardiac aglycones, bile acids, sterols (such as cholesterol), toad poisons, saponins, and some of the carcinogenic hydrocarbons. [EU]

**Stomach:** An organ of digestion situated in the left upper quadrant of the

abdomen between the termination of the esophagus and the beginning of the duodenum. [NIH]

**Systemic:** Pertaining to or affecting the body as a whole. [EU]

**Tetanus:** A disease caused by tetanospasmin, a powerful protein toxin produced by *Clostridium tetani*. Tetanus usually occurs after an acute injury, such as a puncture wound or laceration. Generalized tetanus, the most common form, is characterized by tetanic muscular contractions and hyperreflexia. Localized tetanus presents itself as a mild condition with manifestations restricted to muscles near the wound. It may progress to the generalized form. [NIH]

**Tolerance:** 1. the ability to endure unusually large doses of a drug or toxin. 2. acquired drug tolerance; a decreasing response to repeated constant doses of a drug or the need for increasing doses to maintain a constant response. [EU]

**Transfusion:** The introduction of whole blood or blood component directly into the blood stream. [EU]

**Transplantation:** The grafting of tissues taken from the patient's own body or from another. [EU]

**Tuberculosis:** Any of the infectious diseases of man and other animals caused by species of *Mycobacterium*. [NIH]

**Vaccine:** A suspension of attenuated or killed microorganisms (bacteria, viruses, or rickettsiae), administered for the prevention, amelioration or treatment of infectious diseases. [EU]

**Vaginal:** 1. of the nature of a sheath; ensheathing. 2. pertaining to the vagina. 3. pertaining to the tunica vaginalis testis. [EU]

**Vasculitis:** Inflammation of a vessel, angiitis. [EU]

**Ventricular:** Pertaining to a ventricle. [EU]

**Viruses:** Minute infectious agents whose genomes are composed of DNA or RNA, but not both. They are characterized by a lack of independent metabolism and the inability to replicate outside living host cells. [NIH]



## **PART II: ADDITIONAL RESOURCES AND ADVANCED MATERIAL**

### **ABOUT PART II**

In Part II, we introduce you to additional resources and advanced research on primary immunodeficiency. All too often, parents who conduct their own research are overwhelmed by the difficulty in finding and organizing information. The purpose of the following chapters is to provide you an organized and structured format to help you find additional information resources on primary immunodeficiency. In Part II, as in Part I, our objective is not to interpret the latest advances on primary immunodeficiency or render an opinion. Rather, our goal is to give you access to original research and to increase your awareness of sources you may not have already considered. In this way, you will come across the advanced materials often referred to in pamphlets, books, or other general works. Once again, some of this material is technical in nature, so consultation with a professional familiar with primary immunodeficiency is suggested.





## CHAPTER 4. STUDIES ON PRIMARY IMMUNODEFICIENCY

### Overview

Every year, academic studies are published on primary immunodeficiency or related conditions. Broadly speaking, there are two types of studies. The first are peer reviewed. Generally, the content of these studies has been reviewed by scientists or physicians. Peer-reviewed studies are typically published in scientific journals and are usually available at medical libraries. The second type of studies is non-peer reviewed. These works include summary articles that do not use or report scientific results. These often appear in the popular press, newsletters, or similar periodicals.

In this chapter, we will show you how to locate peer-reviewed references and studies on primary immunodeficiency. We will begin by discussing research that has been summarized and is free to view by the public via the Internet. We then show you how to generate a bibliography on primary immunodeficiency and teach you how to keep current on new studies as they are published or undertaken by the scientific community.

### The Combined Health Information Database

The Combined Health Information Database summarizes studies across numerous federal agencies. To limit your investigation to research studies and primary immunodeficiency, you will need to use the advanced search options. First, go to <http://chid.nih.gov/index.html>. From there, select the "Detailed Search" option (or go directly to that page with the following hyperlink: <http://chid.nih.gov/detail/detail.html>). The trick in extracting studies is found in the drop boxes at the bottom of the search page where

“You may refine your search by.” Select the dates and language you prefer, and the format option “Journal Article.” At the top of the search form, select the number of records you would like to see (we recommend 100) and check the box to display “whole records.” We recommend that you type in “primary immunodeficiency” (or synonyms) into the “For these words:” box. Consider using the option “anywhere in record” to make your search as broad as possible. If you want to limit the search to only a particular field, such as the title of the journal, then select this option in the “Search in these fields” drop box. The following is a sample of what you can expect from this type of search:

- **Nonsunlight Risk Factors for Malignant Melanoma Part II: Immunity, Genetics, and Workplace Prevention**

Source: International Journal of Dermatology. 33(7):462-467, July 1994.

Summary: Malignant melanomas (MM) occur more frequently and act more aggressively in patients with immune dysfunction. The underlying causes of immunodeficiency that have been associated with MM are variable and include primary immunodeficiency, advancing age, association with extracutaneous malignancies, autoimmune disorders, and immunosuppressive therapy. Prospective data show that the incidence of MM in human immunodeficiency virus (HIV)-positive patients is significantly higher than the expected incidence in the general population. Immunohistochemical and monoclonal antibody studies of regional lymph nodes in patients with MM suggest that immunosuppression plays a role in metastatic disease. The existence of hereditary forms of MM suggests that genetic components play a role in its etiology. Parents and offspring of MM patients have approximately a 12-fold increased risk of developing MM. Familial MM, which is defined as 2 or more cases of MM within a kindred, constitutes approximately 10 percent of all patients with MM. As MM gains more recognition as an occupational skin cancer, actions taken by employees and employers will minimize morbidity and mortality. Primary and secondary prevention programs should be adopted by all industries where there is the suggestion that the incidence of MM may be increased. Minimizing or eliminating the MM risks of the indoor and outdoor workplace is important for primary prevention. As for secondary prevention, employers in MM-associated industries have an ideal opportunity to educate employees about their increased risk and to provide them with information about how to do monthly skin self examinations. Larger companies with onsite physicians may incorporate teaching and skin examinations into their role. 96 references.

## Federally-Funded Research on Primary Immunodeficiency

The U.S. Government supports a variety of research studies relating to primary immunodeficiency and associated conditions. These studies are tracked by the Office of Extramural Research at the National Institutes of Health.<sup>19</sup> CRISP (Computerized Retrieval of Information on Scientific Projects) is a searchable database of federally-funded biomedical research projects conducted at universities, hospitals, and other institutions. Visit the site at [http://commons.cit.nih.gov/crisp3/CRISP.Generate\\_Ticket](http://commons.cit.nih.gov/crisp3/CRISP.Generate_Ticket). You can perform targeted searches by various criteria including geography, date, as well as topics related to primary immunodeficiency and related conditions.

For most of the studies, the agencies reporting into CRISP provide summaries or abstracts. As opposed to clinical trial research using patients, many federally-funded studies use animals or simulated models to explore primary immunodeficiency and related conditions. In some cases, therefore, it may be difficult to understand how some basic or fundamental research could eventually translate into medical practice. The following sample is typical of the type of information found when searching the CRISP database for primary immunodeficiency:

- **Project Title: 2002 Summer School in Primary Immunodeficiency Disorders**

Principal Investigator & Institution: Cunningham-Rundles, Charlotte; Associate Professor; Clinical Immunology Society 611 E Wells St, 4Th Fl Milwaukee, Wi 53202

Timing: Fiscal Year 2002; Project Start 1-JUN-2002; Project End 1-MAY-2003

Summary: (provided by applicant): The Clinical Immunology Society is proposing to develop an intensive 3-4 day course on primary immunodeficiency, geared toward fellows in training, with a primary goal of education on the diagnosis, pathogenesis and treatment of primary immunodeficiency diseases. The secondary goals of the course are to attract and develop future scientists in academic medicine; and to enhance the awareness of clinical immunology and its importance in scientific discoveries and clinical application while effectively "mixing" faculty and students in order to break down the "professor/student"

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<sup>19</sup> Healthcare projects are funded by the National Institutes of Health (NIH), Substance Abuse and Mental Health Services (SAMHSA), Health Resources and Services Administration (HRSA), Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDCP), Agency for Healthcare Research and Quality (AHRQ), and Office of Assistant Secretary of Health (OASH).

roles. This course will include seven faculty members and will be presented to 25 fellows. The number of participants is intentionally being planned at a lower level, since this will be an "interactive course." The fellows who participate in this course are to be individuals with responsibility for the evaluation and care of patients with primary immunodeficiency. The candidates will be drawn from training programs, hospitals and institutions that are in North, Central or South America. The program will be advertised on the websites of the Clinical Immunology Society and the Pan American Group for Primary Immunodeficiency. In addition, bulletins will be sent to training directors of Allergy/Immunology programs and Infectious Disease Programs. This course will be held in an informal setting. Day one of the course will have intense lectures and discussion. Day two will again involve intense lectures and discussions. Following the discussion, there will be a testing of the application of knowledge previously presented. Day three will again be comprised of lectures and discussions and will end in the early afternoon. Fellows participating in the program will be expected to present a case to the group for discussion. Faculty members will be paid an honorarium of \$1,000 and have their travel expenses reimbursed for their participation. Fellows participating in the course will be reimbursed for their travel expenses. No registration fee will be charged for the fellows participating in the program.

Website: [http://commons.cit.nih.gov/crisp3/CRISP.Generate\\_Ticket](http://commons.cit.nih.gov/crisp3/CRISP.Generate_Ticket)

- **Project Title: Clinical Investigation of the Patient with Primary Immunodeficiency Disorder**

Principal Investigator & Institution: Wara, Diane W.; Professor of Pediatrics; University of California San Francisco 500 Parnassus Ave San Francisco, Ca 94143

Timing: Fiscal Year 2000

Summary: Diagnosis of inherited immunodeficiency in most children may be categorized as a defect in one or more hematopoietic cell populations based upon standard laboratory measures of cell phenotype and function. However, the precise diagnosis and the underlying pathogenesis of these immune defects remain unknown in many cases. Further understanding of the pathogenesis of inherited immunodeficiencies will lead to improved therapy and an increased understanding of the human immune system.

Website: [http://commons.cit.nih.gov/crisp3/CRISP.Generate\\_Ticket](http://commons.cit.nih.gov/crisp3/CRISP.Generate_Ticket)

- **Project Title: Primary Immunodeficiency Disease Registry**

Principal Investigator & Institution: Winkelstein, Jerry A.; Immune Deficiency Foundation 25 W Chesapeake Ave, Ste 206 Towson, Md 21204

Timing: Fiscal Year 2000; Project Start 8-SEP-1997; Project End 7-SEP-2002

Summary: The purpose of the contract is to support a five year program to establish and maintain a registry of clinical information on U.S. residents affected by primary immunodeficiency diseases. The expected outcomes include: 1) improved access of investigators to patients for both basic studies and clinical trials; 2) provision of accurate and up to date information useful to clinicians and genetic counselors; 3) improved access of affected individuals to the latest therapy; and 4) establishment of a database which can be used to determine the socioeconomic costs of these diseases. Research in several areas will be advanced by this resource include immunodeficiency, host defense against infection, inflammation, and autoimmune diseases.

Website: [http://commons.cit.nih.gov/crisp3/CRISP.Generate\\_Ticket](http://commons.cit.nih.gov/crisp3/CRISP.Generate_Ticket)

- **Project Title: Biological Definition of Host Defense Defects in Man**

Principal Investigator & Institution: Cooper, Max D.; University of Alabama at Birmingham Uab Station Birmingham, Al 35294

Timing: Fiscal Year 2001

Summary: The major goals of this project are to define the defects in lymphocyte differentiation or function associated with immune deficiency diseases, lymphoid malignancies, and disorders of immunoregulation. The underlying thesis is that some of the gaps in knowledge about the human immune system can be addressed by the comparative analysis of the normal ontogeny of the immune system and the immune system defects in primary immunodeficiency diseases. Emphasis is on (1) the ontogeny of B cell development in humans, (2) the genetic basis of immunodeficiency, and (3) the influence of gene defects on the differentiation of immunocompetent cells. X-linked agammaglobulinemia (XLA) remains the prototype of primary immunodeficiency diseases. Although the affected gene underlying XLA has been identified, the molecular mechanisms that lead to the disruption of B cell development is still poorly understood. The hypothesis to be tested is that the block in XLA is not an abrupt termination of cell differentiation between the pre-B and B cell stage, but that deviant development is apparent at earlier stages in pre-B cell development. In previously supported work, evidence of a genetic link between the two most common primary immunodeficiency diseases, IgA deficiency (IgAD) and common variable immunodeficiency (CVID), was obtained.

In the last year, we have shown that in a large family with multiple affected individuals, genetic susceptibility of IgAD or CVID is associated with the inheritance of gene or genes located near the TNF/LT locus within the class III MHC region. The disease phenotype and prevalence of immunodeficiency in the offspring of IgAD/CVID patients differ in individuals who lack the susceptibility MHC haplotype. Analysis of MHC haplotypes in patients and their families to elucidate which gene in the MHC region is associated with these diseases will be continued. Specific candidate genes in and around the TNF/LT locus are being examined in these families.

Website: [http://commons.cit.nih.gov/crisp3/CRISP.Generate\\_Ticket](http://commons.cit.nih.gov/crisp3/CRISP.Generate_Ticket)

- **Project Title: Federation of Clinical Immunology Societies Meeting**

Principal Investigator & Institution: Hafler, David A.; Professor; Clinical Immunology Society 6900 Grove Rd Thorofare, Nj 08086

Timing: Fiscal Year 2001; Project Start 4-MAY-2001; Project End 3-MAY-2002

Summary: (Adapted from Applicant's Abstract) The Clinical Immunology Society (CIS) has undertaken the task of arranging a federated meeting for clinical immunology to be held yearly commencing in May 2001. This new meeting plans to provide an opportunity for members of each of the individual clinical immunology societies involved to meet together on a yearly basis. The first Federated meeting will be held in Boston, May 4-7, 2001. We believe that this new meeting will consolidate the field of Clinical Immunology as it reaches maturity, particularly as it relates to the major human autoimmune diseases including multiple sclerosis, rheumatoid arthritis, and juvenile diabetes. Resultant cross-fertilization from this meeting among the disease-centric investigators and members of the biotech and pharmaceutical community is of critical importance with the increasing numbers of therapeutics for treatment of these autoimmune diseases. This meeting reflects the new interdisciplinary nature now necessary for the investigation and treatment of human autoimmune diseases. It will also cover additional immune based diseases including, but not limited to, asthma, immuno-oncology, acquired immunodeficiency, primary immunodeficiency, transplantation tolerance and immuno-dermatology. Another key aspect will be the inclusion of the Immune Tolerance Network annual meeting. This will provide an important opportunity to inform industry about the Immune Tolerance Network and to disseminate new information about science and medicine. The format will be three days on topics of mutual interest to all constituent groups. There will be two major plenary lectures to begin each day, followed by

concurrent major symposia on topics of interest to constituent groups. Afternoons will be abstract-driven interspersed with breakout meetings for the constituent societies and presentations by biotech and pharmaceutical firms concerning technologies of interest to the assembled groups. There will be two additional meetings held in conjunction with this meeting. The first of these is a "fellows day" in which plenary and abstract driven talks will be held on the day preceding the main scientific sessions. The second parallel session will be on "science for the non-clinician" which targets the lay societies representing the constituent scientific societies.

Website: [http://commons.cit.nih.gov/crisp3/CRISP.Generate\\_Ticket](http://commons.cit.nih.gov/crisp3/CRISP.Generate_Ticket)

- **Project Title: General Clinical Research Center**

Principal Investigator & Institution: Debas, Haile T.; Dean, School of Medicine; Medicine; University of California San Francisco 500 Parnassus Ave San Francisco, Ca 94143

Timing: Fiscal Year 2000; Project Start 1-DEC-1981; Project End 0-NOV-2001

Summary: Continuation of the General Clinical Research Center for children and neonates (PCRC) at the University of California, San Francisco (UCSF) and a satellite outpatient unit at Children's Hospital Oakland (CHO) is proposed in order to provide facilities for multidisciplinary intensive bedside and outpatient clinical investigation of human disease. Support is requested for 591 inpatient A-days and 2476 outpatient A-days in the main facility as well as 257 B-days with ancillaries and 9444 nursing hours in the neonatal satellite unit at UCSF. 1212 outpatient A-days are requested for CHO. A Core Laboratory at UCSF and a satellite HLA-typing Core Laboratory at CHO are proposed. Support is requested for a Computer-based Data Management and Analysis System (CDMAS) and for a statistician to provide essential services for investigators at both UCSF and CHO. The Center and Satellite units provide for hospitalization of patients in a setting in which skilled intensive nursing care, precise collection of blood, urine and stool specimens, as well as other special procedures, can be carried out. Faculty members of the clinical and basic science departments of the School of Medicine at UCSF as well as the School of Dentistry, Nursing and Pharmacy will study problems which include most of the major fields of clinical investigation in Pediatrics. The PCRC provides unique opportunities for the training of students, residents, post-doctoral fellows and junior faculty from all four schools in all aspects of clinical investigation. Major research activities include: pathogenesis and treatment (including gene therapy) of children with primary

immunodeficiency disorders; molecular defect(s) of children with inheritable disease and malignancies; the use of novel agents such as 131 I-metaiodobenzylguanidine for the treatment of patients with advanced neuroblastoma; genetic mutations and outcome in pediatric brain tumors; human papilloma virus infection and cervical cancer in adolescents; growth hormone in children with short stature; GnRH agonists in central precocious puberty; type I diabetes mellitus; non-invasive assessment of cardiac function; pathogenesis and treatment in Pediatric AIDS; Magnetic Resonance Imaging parameters as a predictor of outcome in neonates with CNS hypoxia; maternal cocaine use and neurodevelopment of their infants; r-HuEpo for premature infants to decrease transfusion requirements; collectins in neonatal chronic lung disease; in utero stem cell transplantation inheritable diseases; pathogenesis and treatment in Sickle Cell Disease; nursing investigation in children's responses to pain and nutrition; multi-institutional trials for cancer through the Children's Cancer Study Group, for AIDS through the Pediatric GI consortium.

Website: [http://commons.cit.nih.gov/crisp3/CRISP.Generate\\_Ticket](http://commons.cit.nih.gov/crisp3/CRISP.Generate_Ticket)

- **Project Title: Genetically Determined Immunodeficiencies--Analyses of Defects and Therapies**

Principal Investigator & Institution: Buckley, Rebecca H.; ; Duke University Durham, Nc 27706

Timing: Fiscal Year 2000

Summary: The overall goal of this research is to define the cellular and, ultimately, the molecular bases for both currently recognized and yet to be defined primary immunodeficiency diseases, so as to provide the most rational and effective therapies for them. Correlative studies of lymphocyte phenotypes and function in patients with genetically-determined immunodeficiency will provide clues to as yet undiscovered molecular derangements and also permit the discovery of atypical phenotypes resulting from known mutations. Results: During the current reporting period, we performed 23 stem cell transplants in patients with primary immunodeficiency. The creation of human SCID haploidentical bone marrow stem cell chimeras has allowed us a unique opportunity to examine the cellular and molecular bases of human thymic education. we reviewed stem cell transplants done in the neonatal period. The success rate is 93% success rate for stem cell transplants done in the neonatal period. We conclude that in utero therapy (currently being proposed) is not likely to offer any advantage over this high success rate. We hypothesize that abnormalities in B and NK cell development post-transplantation are related to the underlying molecular defect leading to SCID, and the development of normal B and/or NK cell function is due



to the presence of donor B and/or NK cells or to double parental T cell chimerism. We are finding that diminished numbers of CD4+ T cells and an increase in alpha/beta T cells several years after transplantation in some SCIDs are an indication of incomplete or inadequate T cell reconstitution and/or autoimmune reactions and may signal the need for a booster transplant. The studies proposed take advantage of a unique large population of patients with genetically-determined immunodeficiency diseases who are referred to the investigators at this GCRC. Future plans: Plans for this protocol are to continue to examine patients with primary immunodeficiency for their fundamental abnormalities so that gene therapy might be accomplished when the technology for this becomes perfected. We will continue to characterize all such patients at a cellular level so that consistent phenotypic and functional patterns can be used as an aid in predicting underlying molecular defects, as it did in the case of Jak3 deficiency. Our plans also include the continued study of T and B cell ontogeny, MHC restriction, and tolerance induction in the 75 surviving human SCID bone marrow stem cell chimeras that we have developed over the past 16.5 years. Significance: Bone marrow stem cell transplantation is currently the most successful therapy for all forms of human SCID (82% success rate at this Institution) and will continue to be so until gene therapy becomes perfected. This GCRC protocol has permitted us to become a world leader in this type of transplantation. However, since T cell- depleted haploidentical marrow transplantation was only developed 17 years ago, the long term extent of immune reconstitution is unknown and can only be known through continued and careful longitudinal immunologic studies in these rare and informative infants and children.

Website: [http://commons.cit.nih.gov/crisp3/CRISP.Generate\\_Ticket](http://commons.cit.nih.gov/crisp3/CRISP.Generate_Ticket)

- **Project Title: Identification of Genes that Regulate T Cell Development**

Principal Investigator & Institution: Kaye, Jonathan G.; Associate Professor; Scripps Research Institute 10550 N Torrey Pines Rd San Diego, Ca 92037

Timing: Fiscal Year 2000; Project Start 1-DEC-1998; Project End 0-NOV-2003

Summary: As the site of complex cellular interactions and receptor mediated signaling events that lead to the production of mature T cells, the thymus is a likely target for mutations that result in primary immunodeficiency. Although many cell surface markers are available to delineate the stages of T cell development in the thymus, we know very little about the underlying molecular events that regulate these processes. This is particularly true for positive selection, the differentiation of

developing thymocytes as a consequence of T cell antigen receptor (TCR)- mediated activation. We have assembled a unique set of tools and offer a unique approach to narrow the search for genes that play a critical role in positive selection. Rather than attempt to isolate all genes whose expression is associated with a particular development stage of T cell maturation, our approach is designed to identify genes that are regulated by TCR activation of specific signaling pathways that are required for T cell development. In order to accomplish this, we will take advantage of the immature thymocyte cell line DPK, that we have previously isolated and characterized. These cells maintain the ability to differentiate in culture, and we have shown that this differentiation is both Ras and calcineurin dependent, as is positive selection of normal thymocytes. In addition, DPK cells that express active Ras show a partially differentiated phenotype. Utilizing suppression subtractive hybridization and DPK cells that express active Ras or a dominant negative mutant of Ras, we will isolate genes that are specifically induced by TCR activation of the Ras/MAP kinase pathway in double positive thymocytes. A similar approach is described for isolating genes that are specifically induced by TCR mediated Calcineurin activation. A strategy for screening these differentially expressed sequences for genes that are candidates to play an important role in T cell development is outlined. In vitro gene transgene transfer and transgenic and gene targeting strategies will ultimately be used to determine the function of these genes.

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- **Project Title: Immunobiology Training Grant**

Principal Investigator & Institution: Mayer, Lloyd F.; Professor; Immunobiology Center; Mount Sinai School of Medicine of Nyu of New York University New York, Ny 10029

Timing: Fiscal Year 2001; Project Start 1-JUL-2001; Project End 0-JUN-2006

Summary: (provided by applicant): This training program has been designed to provide pre- and postdoctoral candidates with the individual intellectual and technical skills required becoming outstanding academic scientists in the field of Immunobiology. The aim is to utilize the growth of Immunobiology and the expansion of its faculty at Mount Sinai as a resource to create a fertile environment for the growth of Graduate Students and Postdoctoral Fellows. Each trainee will be exposed not only to direct laboratory research, but will have the opportunity (actually be required) to participate in the educational programs focused on Immunobiology established here at Mount Sinai. For Physician Scientists there will be ample opportunity to immerse themselves in translational

research programs relating to cytokine biology, HIV-related disorders Mucosal Immunology, autoimmunity and Primary Immunodeficiency. There is formal course work, seminar series, journal clubs and work in progress meetings (attended by the entire Immunobiology faculty and trainees). A single faculty member acts as a preceptor for a given fellow or graduate student supervising his/her laboratory work, orchestrating an appropriate training program (e.g. course work), and providing an environment that will help foster maturation towards an independent career in immunobiology research. The program has successfully recruited outstanding trainees from a number of prestigious institutions who have been attracted to Mount Sinai because of the enormous growth in the basic sciences, excellence in research, a protective and nurturing mentoring environment and a clear commitment to student and postdoctoral fellowship training.

Website: [http://commons.cit.nih.gov/crisp3/CRISP.Generate\\_Ticket](http://commons.cit.nih.gov/crisp3/CRISP.Generate_Ticket)

- **Project Title: IVGIV- C with IGIV Solvent for Immune Deficiency**

Principal Investigator & Institution: Ochs, Hans D.; University of Washington 3935 University Way Ne Seattle, Wa 98195

Timing: Fiscal Year 2000

Summary: Immunoglobulin for intravenous (IVIg) has been used for more than 15 years in patients with primary immunodeficiency diseases and has dramatically improved the health status of affected patients. In an effort to improve the quality, effectiveness, and safety of this product, IGIV-C, is purer than the previously licensed product, IGIV-S/D, more closely reflects the IgG subclass distribution found in plasma, and is treated with caprylate rather than solvent-detergent to inactivate viruses such as hepatitis. Preclinical analytical and in vivo animal models have demonstrated the similar physical, chemical and functional properties of IGIV-C to IGIV-S/D. This will be the first clinical trial to compare the pharmacokinetics and safety profile of IGIV-C with IGIV-S/D in patients with primary humoral immune deficiency.

Website: [http://commons.cit.nih.gov/crisp3/CRISP.Generate\\_Ticket](http://commons.cit.nih.gov/crisp3/CRISP.Generate_Ticket)

- **Project Title: Models of Human Immunodeficiencies**

Principal Investigator & Institution: Terhorst, Cornelis P.; ; Beth Israel Deaconess Medical Center 330 Brookline Ave Boston, Ma 02215

Timing: Fiscal Year 2000; Project Start 1-AUG-1994; Project End 1-JUL-2003

Summary: The immune response combines extraordinary specificity of recognition with extremely complex control mechanisms that govern its

effector mechanisms. Childhood primary immunodeficiency disorders can be viewed as experiments of nature in which a discrete genetic defect affects the expression and/or the structure/function of essential lymphocyte proteins and results in immune dysfunctions. A molecular or genetic definition of primary immunodeficiencies is essential for accurate diagnosis and therapy of the disorders and for better understanding of normal immune functions. In this program project, we propose to study a limited set of immunological diseases because of our success in analyzing both patient materials as well as genetic animal models. We will use recently acquired insights into the causes of the X-linked Lympho Proliferative disease (XLP), severe combined immunodeficiencies (SCID), Omenn syndrome and Common Variable Immunodeficiencies caused by T cell signaling defects in the XLP gene and in the critical adapter protein SLP-76. Our genetic animal models will become powerful tools for a systematic dissection of the biochemical processes involved in the pathogenesis of these diseases, but they will also shed light on basic mechanisms that govern ontogeny of the immune system.

Website: [http://commons.cit.nih.gov/crisp3/CRISP.Generate\\_Ticket](http://commons.cit.nih.gov/crisp3/CRISP.Generate_Ticket)

- **Project Title: Molecular Basis of the Hyper IgE Immunodeficiency**

Principal Investigator & Institution: Chatila, Talal A.; Professor; Pediatrics; Washington University Lindell and Skinker Blvd St. Louis, Mo 63130

Timing: Fiscal Year 2000; Project Start 1-AUG-1998; Project End 0-JUN-2003

Summary: (Adapted from Investigator's abstract): Primary immunodeficiency disorders result from genetic defects that leave their human hosts immunocompromised and susceptible to devastating illnesses. Our long term goal is to elucidate the molecular basis of inherited immunodeficiency disorders. The focus of this proposal is to define the role of IL-4 receptor alpha chain (IL-4Ra) mutations in the pathogenesis of the hyper IgE syndrome (HIE), a primary immunodeficiency disorder characterized by serious recurrent infections and high IgE levels. We have identified a gain of function mutation (Q576R) in the cytoplasmic domain of the IL-4Ra chain which is prevalent in patients with HIE syndrome and allergic inflammatory disorders. We hypothesize that this mutation contributes to the pathogenesis of hyper IgE syndrome and related allergic disorders. We propose to establish the mechanism by which the mutant IL-4Ra allele contributes to the pathogenesis of HIE and other allergic inflammatory disorders by studying the interaction of mutant IL-4Ra chain with signaling intermediates both in vitro and using cellular models. We also

propose to develop a transgenic mouse model to study the impact of the mutant IL-4Ra allele on the development of allergic inflammation in murine models of atopy. These studies will provide better understanding of the pathogenesis of HIE and its allied disorders and will facilitate the design of rational therapeutic approaches.

Website: [http://commons.cit.nih.gov/crisp3/CRISP.Generate\\_Ticket](http://commons.cit.nih.gov/crisp3/CRISP.Generate_Ticket)

- **Project Title: Regulation of CA Signaling During Oogenesis**

Principal Investigator & Institution: Machaca, Khaled A.; Physiology and Biophysics; University of Arkansas Med Scis Ltl Rock 4301 W Markham St Little Rock, Ar 72205

Timing: Fiscal Year 2000; Project Start 0-SEP-2000; Project End 1-AUG-2005

Summary: Calcium signaling is mediated by a rise in cytoplasmic calcium, either by calcium release from intracellular stores or calcium influx from the extracellular space. In non-excitable cells, the primary calcium entry pathway is Store Operated Calcium Entry. Calcium is a ubiquitous second messenger that is important for many cellular responses, including gene transcription, fertilization, contraction, secretion, cellular proliferation, and apoptosis. How calcium mediates these different cellular responses, often in the same cell, is not clear. Furthermore, the modulation of calcium signaling during the cell cycle is not well defined. This proposal addresses the regulation and specificity of calcium signaling during *Xenopus* oocyte meiosis. *Xenopus* oocytes provide a good model for these studies because during oocyte maturation, the two primary calcium signaling pathways, namely IP3 dependent calcium release and SOCE, undergo dramatic changes. IP3-dependent calcium release is enhanced several fold and SOCE is somehow inactivated during meiosis. Determining how these calcium signaling pathways are regulated during meiosis will improve our understanding of calcium signal regulation. An additional advantage of *Xenopus* oocytes is that they contain calcium-activated chloride currents that can be used as real time indicators of how different calcium signals affect downstream effectors, thus improving our understanding of calcium signal specificity. The specific aims of the proposal are: 1) characterize the spatial and temporal features of IP3-mediated calcium release and SOCE throughout oogenesis; 2) elucidate the mechanisms regulating SOCE inactivation, and increased IP3-mediated release during meiosis; and 3) record SOCE in mouse oocytes, and test whether it is inactivated during meiosis. In the *Xenopus* oocyte studies, calcium-activated Cl currents will be measured as downstream effectors of calcium signals. Calcium signaling is important for cellular proliferation

and has been implicated in cancer development. Furthermore, SOCE is downregulated in T-cells from patients with primary immunodeficiency, implicating it as an essential signaling pathway in the immune response. Therefore, in addition to contributing to a better basic understanding of calcium signaling, this work will offer insights into the role of calcium signaling in diseases, such as cancer and immunodeficiency.

Website: [http://commons.cit.nih.gov/crisp3/CRISP.Generate\\_Ticket](http://commons.cit.nih.gov/crisp3/CRISP.Generate_Ticket)

- **Project Title: The Pathogenesis of Colitis in a Novel TH2 Model of IBD**

Principal Investigator & Institution: Snapper, Scott B.; Massachusetts General Hospital 55 Fruit St Boston, Ma 02114

Timing: Fiscal Year 2002; Project Start 5-APR-2002; Project End 1-MAR-2005

Summary: (provided by applicant): The overall objective of this project is to gain further understanding of the mucosal immune system and the defects that contribute to the pathogenesis of human inflammatory bowel disease (IBD). The generation of a number of murine models of IBD has facilitated investigation into the basic mechanisms underlying IBD pathogenesis. Despite the fact that most murine models of IBD result from a defect in a single protein known to affect leukocyte function, the specific auto-reactive or regulatory cell population responsible for disease pathogenesis remains unknown. The Wiskott-Aldrich syndrome (WAS) is one of several immunodeficiencies that have been associated with autoimmunity, including IBD. We have recently generated a mouse model of IBD that results from the targeted disruption of the Wiskott-Aldrich syndrome protein (WASP). WASP is expressed solely in hematopoietic cells and is a signaling molecule that regulates cell surface receptor signals to the cytoskeleton. Abnormalities in this protein lead to the rare X-linked primary immunodeficiency that carries its name. The majority of WASP KO (WKO) mice also develop colitis. Our preliminary studies suggest that the colitis in WKO mice is unique, and perhaps more similar to human IBD than other murine models of IBD, because WASP-deficiency does not result in the loss of a specific T-cell class (e.g., alpha-beta T cells) or the absence of one specific cytokine (e.g., IL-2, IL-10). The development of each hematopoietic lineage is intact despite the fact that WASP regulates the actin cytoskeleton in all hematopoietic cells. In contrast with most murine models of IBD that have a Th1 bias, we demonstrate that lymphocytes isolated from the colonic lamina propria of WKO mice secrete a Th2 cytokine pattern. In addition, our genetic and adoptive transfer studies have established the requirement for lymphocytes in disease pathogenesis and the specific ability of CD4<sup>+</sup> T-cells to transfer disease. Furthermore, WKO mice have a reduction in

regulatory T-cells that are known to regulate autoimmunity in mice. Preliminary data also suggests that microbes play an essential role in disease pathogenesis. Interestingly, non-lethal irradiation leads to a dramatic increase in the severity of colitis with 100 percent disease penetrance. Our first aim is to define the role of WASP in regulatory and effector T-cell function and the contribution of additional leukocyte populations in IBD initiation and maintenance. Our second goal is to define the requirement of Th2 cytokines and the role of inflammatory and suppressor cytokines in colitis development. Our final goal of this proposal is to evaluate the role of bacteria and barrier function in colitis initiation in WKO mice. Overall, this project seeks to take advantage of the opportunity to study a murine model of colitis with several unique features that also has a human correlate in order to elucidate the role of cytoskeletal regulation of leukocytes in mucosal homeostasis.

Website: [http://commons.cit.nih.gov/crisp3/CRISP.Generate\\_Ticket](http://commons.cit.nih.gov/crisp3/CRISP.Generate_Ticket)

## E-Journals: PubMed Central<sup>20</sup>

PubMed Central (PMC) is a digital archive of life sciences journal literature developed and managed by the National Center for Biotechnology Information (NCBI) at the U.S. National Library of Medicine (NLM).<sup>21</sup> Access to this growing archive of e-journals is free and unrestricted.<sup>22</sup> To search, go to <http://www.pubmedcentral.nih.gov/index.html#search>, and type "primary immunodeficiency" (or synonyms) into the search box. This search gives you access to full-text articles. The following is a sample of items found for primary immunodeficiency in the PubMed Central database:

- **Pronounced acute immunosuppression in vivo mediated by HIV Tat challenge** by Sandra S. Cohen, Chiang Li, Linna Ding, Yunzhen Cao, Arthur B. Pardee, Ethan M. Shevach, and David I. Cohen; 1999 September 14  
<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=17970>

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<sup>20</sup> Adapted from the National Library of Medicine:  
<http://www.pubmedcentral.nih.gov/about/intro.html>.

<sup>21</sup> With PubMed Central, NCBI is taking the lead in preservation and maintenance of open access to electronic literature, just as NLM has done for decades with printed biomedical literature. PubMed Central aims to become a world-class library of the digital age.

<sup>22</sup> The value of PubMed Central, in addition to its role as an archive, lies the availability of data from diverse sources stored in a common format in a single repository. Many journals already have online publishing operations, and there is a growing tendency to publish material online only, to the exclusion of print.

## The National Library of Medicine: PubMed

One of the quickest and most comprehensive ways to find academic studies in both English and other languages is to use PubMed, maintained by the National Library of Medicine. The advantage of PubMed over previously mentioned sources is that it covers a greater number of domestic and foreign references. It is also free to the public.<sup>23</sup> If the publisher has a Web site that offers full text of its journals, PubMed will provide links to that site, as well as to sites offering other related data. User registration, a subscription fee, or some other type of fee may be required to access the full text of articles in some journals.

To generate your own bibliography of studies dealing with primary immunodeficiency, simply go to the PubMed Web site at **[www.ncbi.nlm.nih.gov/pubmed](http://www.ncbi.nlm.nih.gov/pubmed)**. Type “primary immunodeficiency” (or synonyms) into the search box, and click “Go.” The following is the type of output you can expect from PubMed for “primary immunodeficiency” (hyperlinks lead to article summaries):

- **Use of thymosin in the treatment of primary immunodeficiency diseases and cancer.**

Author(s): Goldstein AL, Cohen GH, Rossio JL, Thurman GB, Brown CN, Ulrich JT.

Source: The Medical Clinics of North America. 1976 May; 60(3): 591-606. No Abstract Available.

[http://www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list\\_uids=131889&dopt=Abstract](http://www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=131889&dopt=Abstract)

## Vocabulary Builder

**Autoimmunity:** Process whereby the immune system reacts against the body's own tissues. Autoimmunity may produce or be caused by autoimmune diseases. [NIH]

**Biochemical:** Relating to biochemistry; characterized by, produced by, or

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<sup>23</sup> PubMed was developed by the National Center for Biotechnology Information (NCBI) at the National Library of Medicine (NLM) at the National Institutes of Health (NIH). The PubMed database was developed in conjunction with publishers of biomedical literature as a search tool for accessing literature citations and linking to full-text journal articles at Web sites of participating publishers. Publishers that participate in PubMed supply NLM with their citations electronically prior to or at the time of publication.



involving chemical reactions in living organisms. [EU]

**Chimera:** An individual that contains cell populations derived from different zygotes. [NIH]

**Cytoskeleton:** The network of filaments, tubules, and interconnecting filamentous bridges which give shape, structure, and organization to the cytoplasm. [NIH]

**Dermatology:** A medical specialty concerned with the skin, its structure, functions, diseases, and treatment. [NIH]

**Haplotypes:** The genetic constitution of individuals with respect to one member of a pair of allelic genes, or sets of genes that are closely linked and tend to be inherited together such as those of the major histocompatibility complex. [NIH]

**Homeostasis:** A tendency to stability in the normal body states (internal environment) of the organism. It is achieved by a system of control mechanisms activated by negative feedback; e.g. a high level of carbon dioxide in extracellular fluid triggers increased pulmonary ventilation, which in turn causes a decrease in carbon dioxide concentration. [EU]

**Humoral:** Of, relating to, proceeding from, or involving a bodily humour - now often used of endocrine factors as opposed to neural or somatic. [EU]

**Hybridization:** The genetic process of crossbreeding to produce a hybrid. Hybrid nucleic acids can be formed by nucleic acid hybridization of DNA and RNA molecules. Protein hybridization allows for hybrid proteins to be formed from polypeptide chains. [NIH]

**Hypoxia:** Reduction of oxygen supply to tissue below physiological levels despite adequate perfusion of the tissue by blood. [EU]

**Malignant:** Tending to become progressively worse and to result in death. Having the properties of anaplasia, invasion, and metastasis; said of tumours. [EU]

**Meiosis:** A special method of cell division, occurring in maturation of the germ cells, by means of which each daughter nucleus receives half the number of chromosomes characteristic of the somatic cells of the species. [NIH]

**Melanoma:** A tumour arising from the melanocytic system of the skin and other organs. When used alone the term refers to malignant melanoma. [EU]

**Neonatal:** Pertaining to the first four weeks after birth. [EU]

**Oocytes:** Female germ cells in stages between the prophase of the first maturation division and the completion of the second maturation division. [NIH]

**Oogenesis:** The formation, development, and maturation of the female germ cell. [NIH]

**Pharmacokinetics:** The action of drugs in the body over a period of time, including the processes of absorption, distribution, localization in tissues, biotransformation, and excretion. [EU]

**Phenotype:** The outward appearance of the individual. It is the product of interactions between genes and between the genotype and the environment. This includes the killer phenotype, characteristic of yeasts. [NIH]

**Puberty:** The period during which the secondary sex characteristics begin to develop and the capability of sexual reproduction is attained. [EU]

**Receptor:** 1. a molecular structure within a cell or on the surface characterized by (1) selective binding of a specific substance and (2) a specific physiologic effect that accompanies the binding, e.g., cell-surface receptors for peptide hormones, neurotransmitters, antigens, complement fragments, and immunoglobulins and cytoplasmic receptors for steroid hormones. 2. a sensory nerve terminal that responds to stimuli of various kinds. [EU]

**Reconstitution:** 1. a type of regeneration in which a new organ forms by the rearrangement of tissues rather than from new formation at an injured surface. 2. the restoration to original form of a substance previously altered for preservation and storage, as the restoration to a liquid state of blood serum or plasma that has been dried and stored. [EU]

**Sclerosis:** A induration, or hardening; especially hardening of a part from inflammation and in diseases of the interstitial substance. The term is used chiefly for such a hardening of the nervous system due to hyperplasia of the connective tissue or to designate hardening of the blood vessels. [EU]

**Solvent:** 1. dissolving; effecting a solution. 2. a liquid that dissolves or that is capable of dissolving; the component of a solution that is present in greater amount. [EU]

**Thymosin:** Thymosin. A family of heat-stable, polypeptide hormones secreted by the thymus gland. Their biological activities include lymphocytopoiesis, restoration of immunological competence and enhancement of expression of T-cell characteristics and function. They have therapeutic potential in patients having primary or secondary immunodeficiency diseases, cancer or diseases related to aging. [NIH]

**Tolerance:** 1. the ability to endure unusually large doses of a drug or toxin. 2. acquired drug tolerance; a decreasing response to repeated constant doses of a drug or the need for increasing doses to maintain a constant response. [EU]

**Xenopus:** An aquatic genus of the family, Pipidae, occurring in Africa and distinguished by having black horny claws on three inner hind toes. [NIH]

## CHAPTER 5. BOOKS ON PRIMARY IMMUNODEFICIENCY

### Overview

This chapter provides bibliographic book references relating to primary immunodeficiency. You have many options to locate books on primary immunodeficiency. The simplest method is to go to your local bookseller and inquire about titles that they have in stock or can special order for you. Some parents, however, prefer online sources (e.g. [www.amazon.com](http://www.amazon.com) and [www.bn.com](http://www.bn.com)). In addition to online booksellers, excellent sources for book titles on primary immunodeficiency include the Combined Health Information Database and the National Library of Medicine. Once you have found a title that interests you, visit your local public or medical library to see if it is available for loan.

### Book Summaries: Online Booksellers

Commercial Internet-based booksellers, such as Amazon.com and Barnes & Noble.com, offer summaries which have been supplied by each title's publisher. Some summaries also include customer reviews. Your local bookseller may have access to in-house and commercial databases that index all published books (e.g. Books in Print®). The following have been recently listed with online booksellers as relating to primary immunodeficiency (sorted alphabetically by title; follow the hyperlink to view more details at Amazon.com):

- **Primary Immunodeficiency Diseases** by Ralph J. Wedgwood (Editor) (1983); ISBN: 0471836044;

<http://www.amazon.com/exec/obidos/ASIN/0471836044/icongroupinterna>

- **Primary Immunodeficiency Diseases (International Congress Series, No 692)** by Martha M. Eibl, Fred S. Rosen (Editor); ISBN: 0444807780; <http://www.amazon.com/exec/obidos/ASIN/0444807780/icongroupinterna>
- **Primary Immunodeficiency Diseases: A Molecular and Genetic Approach** by Hans D. Ochs (Editor), et al; ISBN: 0195104862; <http://www.amazon.com/exec/obidos/ASIN/0195104862/icongroupinterna>

## The National Library of Medicine Book Index

The National Library of Medicine at the National Institutes of Health has a massive database of books published on healthcare and biomedicine. Go to the following Internet site, <http://locatorplus.gov/>, and then select "Search LOCATORplus." Once you are in the search area, simply type "primary immunodeficiency" (or synonyms) into the search box, and select "books only." From there, results can be sorted by publication date, author, or relevance. The following was recently catalogued by the National Library of Medicine:<sup>24</sup>

- **Advantages and disadvantages of integrating STD.** Author: HIV services into existing MCH / FP programs in sub-Saharan Africa / E. Lule, R. Sturgis, S. Ladha; Year: 1998; 1998
- **African response to the challenge of integrating STD.** Author: HIV-AIDS services into family planning programs / W. Kisubi ... [et al.]; Year: 1997; Nairobi, Kenya, Pathfinder International, 1997
- **Community medicine: a global perspective.** Author: E.W. Ebomoyi ... [et al.]; Year: 1998; Belmont, California, Star Publishing Company, 1998

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<sup>24</sup> In addition to LOCATORPlus, in collaboration with authors and publishers, the National Center for Biotechnology Information (NCBI) is adapting biomedical books for the Web. The books may be accessed in two ways: (1) by searching directly using any search term or phrase (in the same way as the bibliographic database PubMed), or (2) by following the links to PubMed abstracts. Each PubMed abstract has a "Books" button that displays a facsimile of the abstract in which some phrases are hypertext links. These phrases are also found in the books available at NCBI. Click on hyperlinked results in the list of books in which the phrase is found. Currently, the majority of the links are between the books and PubMed. In the future, more links will be created between the books and other types of information, such as gene and protein sequences and macromolecular structures. See <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Books>.

- **Immunodeficiency in man and animals.** Author: editor, Daniel Bergsma ... [et al.]; Year: 1975; Huntington, N. Y.: Krieger, 1977, c1975; ISBN: 0882755447  
<http://www.amazon.com/exec/obidos/ASIN/0882755447/icongroupinterna>
- **Immunodeficiency in man and animals. Editor: Daniel Bergsma; scientific editors: Robert A. Good [and] Joanne Finstad; assistant editor: Natalie W. Paul.** Author: International Workshop on the Primary Immunodeficiency Diseases (2d: 1973: St. Petersburg, Fla.); Year: 1975; Sunderland, Mass., Sinauer Associates [c1975]; ISBN: 0878932062  
<http://www.amazon.com/exec/obidos/ASIN/0878932062/icongroupinterna>
- **Integrating STI and HIV.** Author: AIDS services into MCH / FP programs in East and Southern Africa / I. Askew, N. Maggwa, L. Kangas; Year: 1998; 1998
- **Integration of family planning.** Author: MCH with HIV / STD prevention. Programmatic technical guidance. Priority for primary prevention with a focus on high transmitters; Year: 1998; 1998
- **Molecular basis of X-linked human primary immunodeficiency disease.** Author: J. Donald Capra; Year: 1993; [Dallas, Tex.?: University of Texas Southwestern Medical Center?, 1993]
- **Peer education with gang members: protecting life and health. Homies Unidos, El Salvador.** Author: M. Rose-Avila; Year: 1999; Washington, D.C., Pathfinder International, FOCUS on Young Adults, [1999]
- **Primary immunodeficiency diseases: a molecular and genetic approach.** Author: edited by Hans D. Ochs, C.I. Edvard Smith, Jennifer M. Puck; Year: 1999; New York: Oxford University Press, 1999; ISBN: 0195104862 (alk. paper)  
<http://www.amazon.com/exec/obidos/ASIN/0195104862/icongroupinterna>
- **Primary immunodeficiency diseases: international workshop held September 12-15, 1982, at Rosario Resort, Orcas Island, Washington, U.S.A.** Author: sponsored by March of Dimes Birth Defects Foundation; editors, Ralph J. Wedgwood, Fred S. Rosen, and Natalie W. Pa; Year: 1983; New York: Liss, c1983; ISBN: 0845110543  
<http://www.amazon.com/exec/obidos/ASIN/0845110543/icongroupinterna>
- **Primary immunodeficiency diseases: proceedings of the Workshop on Primary Immunodeficiency Diseases, held in Gmunden, Austria, on 19-21 August 1985.** Author: editors, Martha M. Eibl, Fred S. Rosen; Year: 1986; Amsterdam; New York: Excerpta Medica; New York, NY, USA:

Sole distributors for the USA and Canada, Elsevier Science Pub. Co., 1986; ISBN: 0444807780 (U.S.)

<http://www.amazon.com/exec/obidos/ASIN/0444807780/icongroupinterna>

- **Reproductive health costs: literature review.** Author: E.A. Mumford ... [et al.]; Year: 1998; Washington, D.C., Futures Group International, 1998
- **Reproductive health training for primary providers: a sourcebook for curriculum development. Module 6: Providing selected reproductive health services.** Author: L. Sibley; Year: 1997; Chapel Hill, North Carolina, University of North Carolina at Chapel Hill, School of Medicine, Program for International Training in Health [INTRAH], 1997
- **Reproductive tract infections: global impact and priorities for women's reproductive health.** Author: A. Germain ... [et al.]; Year: 1992; New York, New York, Plenum Press, 1992
- **Risk factors and clinical presentation of acute primary human immunodeficiency virus infection in India.** Author: R.C. Bollinger ... [et al.]; Year: 1996; 1996
- **Social mobilization and social marketing in developing communities: lessons for communicators.** Author: N. McKee; Year: 1993; Penang, Malaysia, Southbound, 1993
- **Socioeconomic, demographic and reproductive health profiles of adolescents in SAARC countries.** Author: R.H. Chaudhury ... [et al.]; Year: 1998; Kathmandu, Nepal, United Nations Population Fund [UNFPA], 1998
- **STD services and comprehensive primary health care: the practical implications.** Author: B.N. Maggwa; Year: 1997; 1997
- **STD syndromic management.** Author: I. Hoffman, B. Vuylsteke; Year: 1997; Arlington, Virginia, Family Health International [FHI], AIDS Control and Prevention Project [AIDSCAP], Latin America and Caribbean Regional Office, 1997
- **Strategies and recurrent costs of the first year of the STD programme in Mozambique.** Author: R. Bastos, H. Folgosa, L. Fransen; Year: 1991; 1991
- **Turning the tide. Safe motherhood: a district action manual.** Author: M.T. Feuerstein; Year: 1993; London, England, Macmillan Press, 1993
- **Uganda Delivery of Improved Services for Health evaluation surveys, 1997.** Author: Delivery of Improved Services for Health (DISH), Pathfinder International; MEASURE Evaluation Project, Carolina Population Center; contributors, Charles Katende ... [et al.]; Year: 1999; Chapel Hill, N.C.: MEASURE; Kampala, Uganda: Pathfinder International, [1999]

- **Using a rapid assessment approach to evaluate the quality of care in an integrated program: the experience of the Family Health Division, Ministry of Health, Botswana.** Author: L.S. Maribe ... [et al.]; Year: 1997; Nairobi, Kenya, Population Council, Africa Operations Research and Technical Assistance Project, 1997
- **World Health Organization report on infectious diseases. Removing obstacles to healthy development.** Author: S. Davey; Year: 1999; Geneva, Switzerland, World Health Organization [WHO], 1999

## Chapters on Primary Immunodeficiency

Frequently, primary immunodeficiency will be discussed within a book, perhaps within a specific chapter. In order to find chapters that are specifically dealing with primary immunodeficiency, an excellent source of abstracts is the Combined Health Information Database. You will need to limit your search to book chapters and primary immunodeficiency using the "Detailed Search" option. Go directly to the following hyperlink: <http://chid.nih.gov/detail/detail.html>. To find book chapters, use the drop boxes at the bottom of the search page where "You may refine your search by." Select the dates and language you prefer, and the format option "Book Chapter." By making these selections and typing in "primary immunodeficiency" (or synonyms) into the "For these words:" box, you will only receive results on chapters in books. The following is a typical result when searching for book chapters on primary immunodeficiency:

- **Colitis and Enteritis in Immunocompromised Individuals**

Source: in Bayless, T.M. and Hanauer, S.B. Advanced Therapy of Inflammatory Bowel Disease. Hamilton, Ontario: B.C. Decker Inc. 2001. p. 639-644.

Contact: Available from B.C. Decker Inc. 20 Hughson Street South, P.O. Box 620, L.C.D. 1 Hamilton, Ontario L8N 3K7. (905) 522-7017 or (800) 568-7281. Fax (905) 522-7839. Email: [info@bcdecker.com](mailto:info@bcdecker.com). Website: [www.bcdecker.com](http://www.bcdecker.com). Price: \$129.00 plus shipping and handling. ISBN: 1550091220.

Summary: This chapter on colitis and enteritis (inflammation of the large and small intestines, respectively) is from the second edition of a book devoted to the details of medical, surgical, and supportive management of patients with Crohn's disease (CD) and ulcerative colitis (UC), together known as inflammatory bowel disease (IBD). When patients present with gastrointestinal (GI) disorders that are resistant to conventional therapies

(for example, gluten withdrawal in celiac disease) or autoimmune GI disease, which occurs at a young age, immunoglobulin levels should be measured to rule out immunodeficiency as a cause. Because there is a high prevalence of recurrent giardiasis, sprue-like disorder, NLH (nodular lymphoid hyperplasia, or overgrowth), and IBD in immunodeficient patients, patients with these GI diseases should be screened for hypogammaglobulinemia. Early diagnosis and treatment may reduce the morbidity and mortality associated with immunodeficiency. For immunodeficient patients who present with diarrhea or malabsorption, efforts should be made to seek the cause of these problems, because common causes, such as giardiasis and celiac disease, are treatable. There need not be concerns about treating these patients with potentially immunosuppressive agents (steroids or AZA), because the immunodeficiency is generally controlled with intravenous Ig (immunoglobulins). Owing to the increased risk of malignancy (cancer) in immunodeficient patients, periodic GI evaluation in patients with primary immunodeficiency has been advocated, with a view to early detection and treatment of these malignancies. 2 tables. 10 references.

## General Home References

In addition to references for primary immunodeficiency, you may want a general home medical guide that spans all aspects of home healthcare. The following list is a recent sample of such guides (sorted alphabetically by title; hyperlinks provide rankings, information, and reviews at Amazon.com):

- **American Academy of Pediatrics Guide to Your Child's Symptoms : The Official, Complete Home Reference, Birth Through Adolescence** by Donald Schiff (Editor), et al; Paperback - 256 pages (January 1997), Villard Books; ISBN: 0375752579;  
<http://www.amazon.com/exec/obidos/ASIN/0375752579/icongroupinterna>
- **The Children's Hospital Guide to Your Child's Health and Development** by Alan D. Woolf (Editor), et al; Hardcover - 796 pages, 1st edition (January 15, 2001), Perseus Books; ISBN: 073820241X;  
<http://www.amazon.com/exec/obidos/ASIN/073820241X/icongroupinterna>
- **Helping Your Child in the Hospital: A Practical Guide for Parents** by Nancy Keene, Rachel Prentice; Paperback - 176 pages, 3rd edition (April 15, 2002), O'Reilly & Associates; ISBN: 0596500114;  
<http://www.amazon.com/exec/obidos/ASIN/0596500114/icongroupinterna>



- **Medical Emergencies & Childhood Illnesses: Includes Your Child's Personal Health Journal (Parent Smart)** by Penny A. Shore, William Sears (Contributor); Paperback - 115 pages (February 2002), Parent Kit Corporation; ISBN: 1896833187;  
<http://www.amazon.com/exec/obidos/ASIN/1896833187/icongroupinterna>
- **Taking Care of Your Child: A Parent's Guide to Complete Medical Care** by Robert H. Pantell, M.D., et al; Paperback - 524 pages, 6th edition (March 5, 2002), Perseus Press; ISBN: 0738206016;  
<http://www.amazon.com/exec/obidos/ASIN/0738206016/icongroupinterna>

## Vocabulary Builder

**Enteritis:** Inflammation of the intestine, applied chiefly to inflammation of the small intestine; see also enterocolitis. [EU]

**Epidemic:** Occurring suddenly in numbers clearly in excess of normal expectancy; said especially of infectious diseases but applied also to any disease, injury, or other health-related event occurring in such outbreaks. [EU]

**Giardiasis:** An infection of the small intestine caused by the flagellated protozoan giardia lamblia. It is spread via contaminated food and water and by direct person-to-person contact. [NIH]

**Gluten:** The protein of wheat and other grains which gives to the dough its tough elastic character. [EU]

**Hyperplasia:** The abnormal multiplication or increase in the number of normal cells in normal arrangement in a tissue. [EU]

**Malabsorption:** Impaired intestinal absorption of nutrients. [EU]

**Mobilization:** The process of making a fixed part or stored substance mobile, as by separating a part from surrounding structures to make it accessible for an operative procedure or by causing release into the circulation for body use of a substance stored in the body. [EU]

**Withdrawal:** 1. a pathological retreat from interpersonal contact and social involvement, as may occur in schizophrenia, depression, or schizoid avoidant and schizotypal personality disorders. 2. (DSM III-R) a substance-specific organic brain syndrome that follows the cessation of use or reduction in intake of a psychoactive substance that had been regularly used to induce a state of intoxication. [EU]



## **CHAPTER 6. PERIODICALS AND NEWS ON PRIMARY IMMUNODEFICIENCY**

### **Overview**

Keeping up on the news relating to primary immunodeficiency can be challenging. Subscribing to targeted periodicals can be an effective way to stay abreast of recent developments on primary immunodeficiency. Periodicals include newsletters, magazines, and academic journals.

In this chapter, we suggest a number of news sources and present various periodicals that cover primary immunodeficiency beyond and including those which are published by parent associations mentioned earlier. We will first focus on news services, and then on periodicals. News services, press releases, and newsletters generally use more accessible language, so if you do chose to subscribe to one of the more technical periodicals, make sure that it uses language you can easily follow.

### **News Services & Press Releases**

Well before articles show up in newsletters or the popular press, they may appear in the form of a press release or a public relations announcement. One of the simplest ways of tracking press releases on primary immunodeficiency is to search the news wires. News wires are used by professional journalists, and have existed since the invention of the telegraph. Today, there are several major “wires” that are used by companies, universities, and other organizations to announce new medical breakthroughs. In the following sample of sources, we will briefly describe

how to access each service. These services only post recent news intended for public viewing.

### **PR Newswire**

Perhaps the broadest of the wires is PR Newswire Association, Inc. To access this archive, simply go to <http://www.prnewswire.com>. Below the search box, select the option "The last 30 days." In the search box, type "primary immunodeficiency" or synonyms. The search results are shown by order of relevance. When reading these press releases, do not forget that the sponsor of the release may be a company or organization that is trying to sell a particular product or therapy. Their views, therefore, may be biased.

### **Reuters**

The Reuters' Medical News database can be very useful in exploring news archives relating to primary immunodeficiency. While some of the listed articles are free to view, others can be purchased for a nominal fee. To access this archive, go to <http://www.reutershealth.com/frame2/arch.html> and search by "primary immunodeficiency" (or synonyms). The following was recently listed in this archive for primary immunodeficiency:

- **ZLB awarded \$30 million US supply contract for immunoglobulin products**  
 Source: Reuters Industry Breifing  
 Date: September 10, 2001  
<http://www.reuters.gov/archive/2001/09/10/business/links/20010910inds016.html>
- **Disney's "Bubble Boy" a bitter pill for sufferers**  
 Source: Reuters Health eLine  
 Date: August 15, 2001  
<http://www.reuters.gov/archive/2001/08/15/eline/links/20010815elin021.html>
- **Doctors appeal to ZLB Bioplasma to restore supplies of immunoglobulin**  
 Source: Reuters Industry Breifing  
 Date: February 06, 2001  
<http://www.reuters.gov/archive/2001/02/06/business/links/20010206prof001.html>

- **Baxter recalls single lot of Iveegam EN**  
 Source: Reuters Industry Breifing  
 Date: October 27, 2000  
<http://www.reuters.gov/archive/2000/10/27/business/links/20001027rglt001.html>
- **CDC urges physicians to review use of immune globulin IV products**  
 Source: Reuters Medical News  
 Date: March 05, 1999  
<http://www.reuters.gov/archive/1999/03/05/professional/links/19990305epid002.html>
- **Life-saving immune globulin in short supply**  
 Source: Reuters Health eLine  
 Date: March 04, 1999  
<http://www.reuters.gov/archive/1999/03/04/eline/links/19990304elin007.html>
- **Patients On Corticosteroids For Connective Tissue Diseases At Risk For P. carinii Pneumonia**  
 Source: Reuters Medical News  
 Date: July 29, 1997  
<http://www.reuters.gov/archive/1997/07/29/professional/links/19970729clin002.html>
- **Hepatitis G Infection Rate High, But Transmissibility In Blood Products Low**  
 Source: Reuters Medical News  
 Date: November 19, 1996  
<http://www.reuters.gov/archive/1996/11/19/professional/links/19961119epid001.html>
- **New Genetic Defect May Shed Light On Early Stages Of B Cell Differentiation**  
 Source: Reuters Medical News  
 Date: October 14, 1996  
<http://www.reuters.gov/archive/1996/10/14/professional/links/19961014scie002.html>
- **High Engraftment Rate Seen With In Utero Bone Marrow Transplantation**  
 Source: Reuters Medical News  
 Date: February 09, 1996  
<http://www.reuters.gov/archive/1996/02/09/professional/links/19960209clin011.html>

### **The NIH**

Within MEDLINEplus, the NIH has made an agreement with the New York Times Syndicate, the AP News Service, and Reuters to deliver news that can be browsed by the public. Search news releases at **[http://www.nlm.nih.gov/medlineplus/alphanews\\_a.html](http://www.nlm.nih.gov/medlineplus/alphanews_a.html)**. MEDLINEplus allows you to browse across an alphabetical index. Or you can search by date at **<http://www.nlm.nih.gov/medlineplus/newsbydate.html>**. Often, news items are indexed by MEDLINEplus within their search engine.

### **Business Wire**

Business Wire is similar to PR Newswire. To access this archive, simply go to **<http://www.businesswire.com>**. You can scan the news by industry category or company name.

### **Internet Wire**

Internet Wire is more focused on technology than the other wires. To access this site, go to **<http://www.internetwire.com>** and use the “Search Archive” option. Type in “primary immunodeficiency” (or synonyms). As this service is oriented to technology, you may wish to search for press releases covering diagnostic procedures or tests that you may have read about.

### **Search Engines**

Free-to-view news can also be found in the news section of your favorite search engines (see the health news page at Yahoo: **[http://dir.yahoo.com/Health/News\\_and\\_Media/](http://dir.yahoo.com/Health/News_and_Media/)**, or use this Web site’s general news search page **<http://news.yahoo.com/>**. Type in “primary immunodeficiency” (or synonyms). If you know the name of a company that is relevant to primary immunodeficiency, you can go to any stock trading Web site (such as **[www.etrade.com](http://www.etrade.com)**) and search for the company name there. News items across various news sources are reported on indicated hyperlinks.

## BBC

Covering news from a more European perspective, the British Broadcasting Corporation (BBC) allows the public free access to their news archive located at <http://www.bbc.co.uk/>. Search by “primary immunodeficiency” (or synonyms).

## Newsletters on Primary Immunodeficiency

Given their focus on current and relevant developments, newsletters are often more useful to parents than academic articles. You can find newsletters using the Combined Health Information Database (CHID). You will need to use the “Detailed Search” option. To access CHID, go directly to the following hyperlink: <http://chid.nih.gov/detail/detail.html>. Your investigation must limit the search to “Newsletter” and “primary immunodeficiency.” Go to the bottom of the search page where “You may refine your search by.” Select the dates and language that you prefer. For the format option, select “Newsletter.” By making these selections and typing in “primary immunodeficiency” or synonyms into the “For these words:” box, you will only receive results on newsletters. The following list was generated using the options described above:

- **AAKP Patient Plan. Phase 4: Ongoing Treatment**

Source: AAKP Patient Plan Newsletter. 1(4): 1-12. 2001.

Contact: Available from American Association of Kidney Patients (AAKP). 100 South Ashley Drive, Suite 280, Tampa, FL 33602. (800) 749-AAKP or (813) 223-7099. E-mail: [AAKPnat@aol.com](mailto:AAKPnat@aol.com). Website: [www.aakp.org](http://www.aakp.org).

Summary: This newsletter accompanies and supports the final part of a four phase series of instructional materials for kidney patients. Created by the American Association of Kidney Patients (AAKP), this series is designed to address questions and concerns at various phases of the disease process. The four phases covered are diagnosis and treatment options, access and initiation, stabilization, and ongoing treatment. During each of these phases, the patient can keep control of his or her life by staying active and learning as much as possible about kidney disease and treatment. This newsletter focuses on strategies to maintain good health during ongoing treatment for kidney disease. Articles include one woman's experiences of 10 years with a kidney transplant; the importance of empowerment; strategies for coping with all the pills and

medications required for long term immunosuppression; answers to questions about phosphorus binders (drugs used to help keep normal phosphorus and calcium levels in the blood); and transplantation, pregnancy, and childbirth. One sidebar lists relevant web sites for more information. The newsletter concludes with a glossary of terms, blank space to record questions to ask one's health care provider, and a form for joining the AAKP. The newsletter encourages readers to educate themselves and become active members of their own health care team. There are quotes and suggestions from other kidney patients sprinkled throughout the articles. The newsletter is illustrated with black and white photographs.

## Newsletter Articles

If you choose not to subscribe to a newsletter, you can nevertheless find references to newsletter articles. We recommend that you use the Combined Health Information Database, while limiting your search criteria to "newsletter articles." Again, you will need to use the "Detailed Search" option. Go to the following hyperlink: <http://chid.nih.gov/detail/detail.html>. Go to the bottom of the search page where "You may refine your search by." Select the dates and language that you prefer. For the format option, select "Newsletter Article."

By making these selections, and typing in "primary immunodeficiency" (or synonyms) into the "For these words:" box, you will only receive results on newsletter articles. You should check back periodically with this database as it is updated every 3 months. The following is a typical result when searching for newsletter articles on primary immunodeficiency:

- **Therapy-Treatment of Systemic Sclerosis**

Source: Scleroderma Voice. p. 12-14. Winter 2000-2001.

Contact: Available from Scleroderma Foundation. 12 Kent Way, Suite 101, Byfield, MA 01922. (800) 722-HOPE or (978) 463-5843. Fax (978) 463-5809. E-mail: [sfinfo@scleroderma.org](mailto:sfinfo@scleroderma.org). Website: [www.scleroderma.org](http://www.scleroderma.org).

Summary: This newsletter article provides health professionals and people who have scleroderma with information on approaches to treating systemic sclerosis (SSc). Interrupting the pathogenetic cycle is a reasonable approach to the treatment of SSc. Treatment might be aimed at addressing the vascular damage, preventing fibrosis, or suppressing



the immune response. The article highlights the results of recent clinical trials of a prostacyclin derivative, iloprost, interferon gamma, D-penicillamine, chlorambucil, cyclosporine A, methotrexate, and cyclophosphamide. In general, these trials support the use of prostacyclin derivatives, antifibrotic regimens, and immunosuppressive agents to treat SSc. A more definitive test of the usefulness of immunosuppression for SSc is a trial of stem cell transplantation (SCT). Although SCT results have been encouraging, there has been almost a 25 percent mortality rate among SCT treated patients.

- **Questions and Answers: Infection Risks Post-Transplant**

Source: CLASS Notes. p. 5-6. Spring 1998.

Contact: Available from Children's Liver Association for Support Services (C.L.A.S.S.). 26444 Emerald Dove Drive, Valencia, CA 91355. (877) 689-8256. (661) 255-0353. E-mail: [info@classkids.org](mailto:info@classkids.org). Website: [www.classkids.org](http://www.classkids.org).

Summary: This newsletter article answers the concerns of one parent who writes to ask how to handle infection control in her daughter after the child receives a liver transplant. The parent is worried that drugs given to the child to prevent rejection of her new liver will leave her vulnerable to infectious diseases. The physician who addresses these concerns notes that precautions against infection must be individualized for each patient. Different patients are on different amounts of immunosuppression, and the more immunosuppression a patient has received the more precautions are necessary. Since the chance of rejection is highest during the first 3 months after a transplant, higher doses of immunosuppression are used, and therefore the risk of infection is highest during this time period. The most common infections after a transplant are viral infection; bacterial infections are also fairly common after a transplant (but most can be easily treated with antibiotics). The article concludes with a discussion of chicken pox, a viral infection that requires special consideration. If the patient is immune to chicken pox, the likelihood of having a problem later on is much less since this virus generally causes chicken pox only once. A vaccine is available for chicken pox and many transplant centers are starting to vaccinate children who will some day need a transplant in order to general immunity and prevent future infections. The vaccine is a live virus though, so it cannot be given once the child is on immunosuppression. Other topics covered in the article are childcare, having pets, and the types of immunosuppressant drugs that are usually prescribed.

## Academic Periodicals covering Primary Immunodeficiency

Academic periodicals can be a highly technical yet valuable source of information on primary immunodeficiency. We have compiled the following list of periodicals known to publish articles relating to primary immunodeficiency and which are currently indexed within the National Library of Medicine's PubMed database (follow hyperlinks to view more information, summaries, etc., for each). In addition to these sources, to keep current on articles written on primary immunodeficiency published by any of the periodicals listed below, you can simply follow the hyperlink indicated or go to the following Web site: **[www.ncbi.nlm.nih.gov/pubmed](http://www.ncbi.nlm.nih.gov/pubmed)**. Type the periodical's name into the search box to find the latest studies published.

If you want complete details about the historical contents of a periodical, you can also visit **<http://www.ncbi.nlm.nih.gov/entrez/jrbrowser.cgi>**. Here, type in the name of the journal or its abbreviation, and you will receive an index of published articles. At **<http://locatorplus.gov/>** you can retrieve more indexing information on medical periodicals (e.g. the name of the publisher). Select the button "Search LOCATORplus." Then type in the name of the journal and select the advanced search option "Journal Title Search." The following is a sample of periodicals which publish articles on primary immunodeficiency:

- **The Medical Clinics of North America. (Med Clin North Am)**  
<http://www.ncbi.nlm.nih.gov/entrez/jrbrowser.cgi?field=0&regexp=The+Medical+Clinics+of+North+America&dispmax=20&dispstart=0>

## Vocabulary Builder

**Adjuvant:** A substance which aids another, such as an auxiliary remedy; in immunology, nonspecific stimulator (e.g., BCG vaccine) of the immune response. [EU]

**Cyclophosphamide:** Precursor of an alkylating nitrogen mustard antineoplastic and immunosuppressive agent that must be activated in the liver to form the active aldophosphamide. It is used in the treatment of lymphomas, leukemias, etc. Its side effect, alopecia, has been made use of in defleecing sheep. Cyclophosphamide may also cause sterility, birth defects, mutations, and cancer. [NIH]

**Hematology:** A subspecialty of internal medicine concerned with morphology, physiology, and pathology of the blood and blood-forming tissues. [NIH]

**Iloprost:** An eicosanoid, derived from the cyclooxygenase pathway of arachidonic acid metabolism. It is a stable and synthetic analog of epoprostenol, but with a longer half-life than the parent compound. Its actions are similar to prostacyclin. Iloprost produces vasodilation and inhibits platelet aggregation. [NIH]

**Immunosuppressant:** An agent capable of suppressing immune responses. [EU]

**Methotrexate:** An antineoplastic antimetabolite with immunosuppressant properties. It is an inhibitor of dihydrofolate reductase and prevents the formation of tetrahydrofolate, necessary for synthesis of thymidylate, an essential component of DNA. [NIH]

**Penicillamine:** 3-Mercapto-D-valine. The most characteristic degradation product of the penicillin antibiotics. It is used as an antirheumatic and as a chelating agent in Wilson's disease. [NIH]

**Vascular:** Pertaining to blood vessels or indicative of a copious blood supply. [EU]



## CHAPTER 7. PHYSICIAN GUIDELINES AND DATABASES

### Overview

Doctors and medical researchers rely on a number of information sources to help children with primary immunodeficiency. Many will subscribe to journals or newsletters published by their professional associations or refer to specialized textbooks or clinical guides published for the medical profession. In this chapter, we focus on databases and Internet-based guidelines created or written for this professional audience.

### NIH Guidelines

For the more common medical conditions, the National Institutes of Health publish guidelines that are frequently consulted by physicians. Publications are typically written by one or more of the various NIH Institutes. For physician guidelines, commonly referred to as “clinical” or “professional” guidelines, you can visit the following Institutes:

- Office of the Director (OD); guidelines consolidated across agencies available at **<http://www.nih.gov/health/consumer/conkey.htm>**
- National Institute of General Medical Sciences (NIGMS); fact sheets available at **<http://www.nigms.nih.gov/news/facts/>**
- National Library of Medicine (NLM); extensive encyclopedia (A.D.A.M., Inc.) with guidelines:  
**<http://www.nlm.nih.gov/medlineplus/healthtopics.html>**

- National Institute of Child Health and Human Development (NICHD); guidelines available at <http://www.nichd.nih.gov/publications/pubskey.cfm>

## NIH Databases

In addition to the various Institutes of Health that publish professional guidelines, the NIH has designed a number of databases for professionals.<sup>25</sup> Physician-oriented resources provide a wide variety of information related to the biomedical and health sciences, both past and present. The format of these resources varies. Searchable databases, bibliographic citations, full text articles (when available), archival collections, and images are all available. The following are referenced by the National Library of Medicine:<sup>26</sup>

- **Bioethics:** Access to published literature on the ethical, legal and public policy issues surrounding healthcare and biomedical research. This information is provided in conjunction with the Kennedy Institute of Ethics located at Georgetown University, Washington, D.C.: [http://www.nlm.nih.gov/databases/databases\\_bioethics.html](http://www.nlm.nih.gov/databases/databases_bioethics.html)
- **HIV/AIDS Resources:** Describes various links and databases dedicated to HIV/ AIDS research: <http://www.nlm.nih.gov/pubs/factsheets/aidsinfs.html>
- **NLM Online Exhibitions:** Describes "Exhibitions in the History of Medicine": <http://www.nlm.nih.gov/exhibition/exhibition.html>. Additional resources for historical scholarship in medicine: <http://www.nlm.nih.gov/hmd/hmd.html>
- **Biotechnology Information:** Access to public databases. The National Center for Biotechnology Information conducts research in computational biology, develops software tools for analyzing genome data, and disseminates biomedical information for the better understanding of molecular processes affecting human health and disease: <http://www.ncbi.nlm.nih.gov/>
- **Population Information:** The National Library of Medicine provides access to worldwide coverage of population, family planning, and related health issues, including family planning technology and programs,

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<sup>25</sup> Remember, for the general public, the National Library of Medicine recommends the databases referenced in MEDLINEplus (<http://medlineplus.gov/> or <http://www.nlm.nih.gov/medlineplus/databases.html>).

<sup>26</sup> See <http://www.nlm.nih.gov/databases/databases.html>.

fertility, and population law and policy:

[http://www.nlm.nih.gov/databases/databases\\_population.html](http://www.nlm.nih.gov/databases/databases_population.html)

- **Cancer Information:** Access to cancer-oriented databases:  
[http://www.nlm.nih.gov/databases/databases\\_cancer.html](http://www.nlm.nih.gov/databases/databases_cancer.html)
- **Profiles in Science:** Offering the archival collections of prominent twentieth-century biomedical scientists to the public through modern digital technology: <http://www.profiles.nlm.nih.gov/>
- **Chemical Information:** Provides links to various chemical databases and references: <http://sis.nlm.nih.gov/Chem/ChemMain.html>
- **Clinical Alerts:** Reports the release of findings from the NIH-funded clinical trials where such release could significantly affect morbidity and mortality: [http://www.nlm.nih.gov/databases/alerts/clinical\\_alerts.html](http://www.nlm.nih.gov/databases/alerts/clinical_alerts.html)
- **Space Life Sciences:** Provides links and information to space-based research (including NASA):  
[http://www.nlm.nih.gov/databases/databases\\_space.html](http://www.nlm.nih.gov/databases/databases_space.html)
- **MEDLINE:** Bibliographic database covering the fields of medicine, nursing, dentistry, veterinary medicine, the healthcare system, and the pre-clinical sciences:  
[http://www.nlm.nih.gov/databases/databases\\_medline.html](http://www.nlm.nih.gov/databases/databases_medline.html)
- **Toxicology and Environmental Health Information (TOXNET):** Databases covering toxicology and environmental health:  
<http://sis.nlm.nih.gov/Tox/ToxMain.html>
- **Visible Human Interface:** Anatomically detailed, three-dimensional representations of normal male and female human bodies:  
[http://www.nlm.nih.gov/research/visible/visible\\_human.html](http://www.nlm.nih.gov/research/visible/visible_human.html)

While all of the above references may be of interest to physicians who study and treat primary immunodeficiency, the following are particularly noteworthy.

### The Combined Health Information Database

A comprehensive source of information on clinical guidelines written for professionals is the Combined Health Information Database. You will need to limit your search to “Brochure/Pamphlet,” “Fact Sheet,” or “Information Package” and primary immunodeficiency using the “Detailed Search” option. Go to the following hyperlink: <http://chid.nih.gov/detail/detail.html>. To find associations, use the drop boxes at the bottom of the search page where “You may refine your search by.” For the publication date, select “All

Years,” select your preferred language, and the format option “Fact Sheet.” By making these selections and typing “primary immunodeficiency” (or synonyms) into the “For these words:” box above, you will only receive results on fact sheets dealing with primary immunodeficiency. The following is a sample result:

- **Primary Immune Deficiency Diseases: A Guide for Nurses**

Source: Towson, MD: Immune Deficiency Foundation (IDF). 1992. 21 p.

Contact: Available from Immune Deficiency Foundation (IDF). 25 West Chesapeake Avenue, Suite 206, Towson, MD 21204. (410) 321-6647 or (800) 296-4433; FAX (410) 321-9165. PRICE: Free.

Summary: This guide is intended to assist nurses in detecting primary immune deficiency diseases and providing comprehensive care for patients with these diseases. The guide discusses the physiology of the immune system, the different classes of primary immunodeficiency diseases, the nursing assessment process, diagnostic tests, steps in planning and implementing nursing care, and services to support families of children with immunodeficiency diseases. A bibliography and a brief description of the Immune Deficiency Foundation (IDF) are included.

### **The NLM Gateway<sup>27</sup>**

The NLM (National Library of Medicine) Gateway is a Web-based system that lets users search simultaneously in multiple retrieval systems at the U.S. National Library of Medicine (NLM). It allows users of NLM services to initiate searches from one Web interface, providing “one-stop searching” for many of NLM's information resources or databases.<sup>28</sup> One target audience for the Gateway is the Internet user who is new to NLM's online resources and does not know what information is available or how best to search for it. This audience may include physicians and other healthcare providers, researchers, librarians, students, and, increasingly, parents and the public.<sup>29</sup>

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<sup>27</sup> Adapted from NLM: <http://gateway.nlm.nih.gov/gw/Cmd?Overview.x>.

<sup>28</sup> The NLM Gateway is currently being developed by the Lister Hill National Center for Biomedical Communications (LHNCBC) at the National Library of Medicine (NLM) of the National Institutes of Health (NIH).

<sup>29</sup> Other users may find the Gateway useful for an overall search of NLM's information resources. Some searchers may locate what they need immediately, while others will utilize the Gateway as an adjunct tool to other NLM search services such as PubMed® and MEDLINEplus®. The Gateway connects users with multiple NLM retrieval systems while also providing a search interface for its own collections. These collections include various types of information that do not logically belong in PubMed, LOCATORplus, or other



To use the NLM Gateway, simply go to the search site at <http://gateway.nlm.nih.gov/gw/Cmd>. Type “primary immunodeficiency” (or synonyms) into the search box and click “Search.” The results will be presented in a tabular form, indicating the number of references in each database category.

### Results Summary

| Category                           | Items Found |
|------------------------------------|-------------|
| Journal Articles                   | 9852        |
| Books / Periodicals / Audio Visual | 511         |
| Consumer Health                    | 52          |
| Meeting Abstracts                  | 1254        |
| Other Collections                  | 37          |
| Total                              | 11706       |

### HSTAT<sup>30</sup>

HSTAT is a free, Web-based resource that provides access to full-text documents used in healthcare decision-making.<sup>31</sup> HSTAT's audience includes healthcare providers, health service researchers, policy makers, insurance companies, consumers, and the information professionals who serve these groups. HSTAT provides access to a wide variety of publications, including clinical practice guidelines, quick-reference guides for clinicians, consumer health brochures, evidence reports and technology assessments from the Agency for Healthcare Research and Quality (AHRQ), as well as AHRQ's Put Prevention Into Practice.<sup>32</sup> Simply search by “primary

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established NLM retrieval systems (e.g., meeting announcements and pre-1966 journal citations). The Gateway will provide access to the information found in an increasing number of NLM retrieval systems in several phases.

<sup>30</sup> Adapted from HSTAT: <http://www.nlm.nih.gov/pubs/factsheets/hstat.html>.

<sup>31</sup> The HSTAT URL is <http://hstat.nlm.nih.gov/>.

<sup>32</sup> Other important documents in HSTAT include: the National Institutes of Health (NIH) Consensus Conference Reports and Technology Assessment Reports; the HIV/AIDS Treatment Information Service (ATIS) resource documents; the Substance Abuse and Mental Health Services Administration's Center for Substance Abuse Treatment (SAMHSA/CSAT) Treatment Improvement Protocols (TIP) and Center for Substance Abuse Prevention (SAMHSA/CSAP) Prevention Enhancement Protocols System (PEPS); the Public Health Service (PHS) Preventive Services Task Force's *Guide to Clinical Preventive Services*; the independent, nonfederal Task Force on Community Services *Guide to Community Preventive Services*; and the Health Technology Advisory Committee (HTAC) of the Minnesota Health Care Commission (MHCC) health technology evaluations.

immunodeficiency" (or synonyms) at the following Web site: <http://text.nlm.nih.gov>.

### Coffee Break: Tutorials for Biologists<sup>33</sup>

Some parents may wish to have access to a general healthcare site that takes a scientific view of the news and covers recent breakthroughs in biology that may one day assist physicians in developing treatments. To this end, we recommend "Coffee Break," a collection of short reports on recent biological discoveries. Each report incorporates interactive tutorials that demonstrate how bioinformatics tools are used as a part of the research process. Currently, all Coffee Breaks are written by NCBI staff.<sup>34</sup> Each report is about 400 words and is usually based on a discovery reported in one or more articles from recently published, peer-reviewed literature.<sup>35</sup> This site has new articles every few weeks, so it can be considered an online magazine of sorts, and intended for general background information. Access the Coffee Break Web site at <http://www.ncbi.nlm.nih.gov/Coffeekbreak/>.

### Other Commercial Databases

In addition to resources maintained by official agencies, other databases exist that are commercial ventures addressing medical professionals. Here are a few examples that may interest you:

- **CliniWeb International:** Index and table of contents to selected clinical information on the Internet; see <http://www.ohsu.edu/clinweb/>.
- **Image Engine:** Multimedia electronic medical record system that integrates a wide range of digitized clinical images with textual data stored in the University of Pittsburgh Medical Center's MARS electronic medical record system; see the following Web site: <http://www.cml.upmc.edu/cml/imageengine/imageEngine.html>.

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<sup>33</sup> Adapted from <http://www.ncbi.nlm.nih.gov/Coffeekbreak/Archive/FAQ.html>.

<sup>34</sup> The figure that accompanies each article is frequently supplied by an expert external to NCBI, in which case the source of the figure is cited. The result is an interactive tutorial that tells a biological story.

<sup>35</sup> After a brief introduction that sets the work described into a broader context, the report focuses on how a molecular understanding can provide explanations of observed biology and lead to therapies for diseases. Each vignette is accompanied by a figure and hypertext links that lead to a series of pages that interactively show how NCBI tools and resources are used in the research process.

- **Medical World Search:** Searches full text from thousands of selected medical sites on the Internet; see <http://www.mwsearch.com/>.
- **MedWeaver:** Prototype system that allows users to search differential diagnoses for any list of signs and symptoms, to search medical literature, and to explore relevant Web sites; see <http://www.med.virginia.edu/~wmd4n/medweaver.html>.
- **Metaphrase:** Middleware component intended for use by both caregivers and medical records personnel. It converts the informal language generally used by caregivers into terms from formal, controlled vocabularies; see the following Web site: <http://www.lexical.com/Metaphrase.html>.

## The Genome Project and Primary Immunodeficiency

With all the discussion in the press about the Human Genome Project, it is only natural that physicians, researchers, and parents want to know about how human genes relate to primary immunodeficiency. In the following section, we will discuss databases and references used by physicians and scientists who work in this area.

### Online Mendelian Inheritance in Man (OMIM)

The Online Mendelian Inheritance in Man (OMIM) database is a catalog of human genes and genetic disorders authored and edited by Dr. Victor A. McKusick and his colleagues at Johns Hopkins and elsewhere. OMIM was developed for the World Wide Web by the National Center for Biotechnology Information (NCBI).<sup>36</sup> The database contains textual information, pictures, and reference information. It also contains copious links to NCBI's Entrez database of MEDLINE articles and sequence information.

Go to <http://www.ncbi.nlm.nih.gov/Omim/searchomim.html> to search the database. Type "primary immunodeficiency" (or synonyms) in the search box, and click "Submit Search." If too many results appear, you can narrow the search by adding the word "clinical." Each report will have additional

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<sup>36</sup> Adapted from <http://www.ncbi.nlm.nih.gov/>. Established in 1988 as a national resource for molecular biology information, NCBI creates public databases, conducts research in computational biology, develops software tools for analyzing genome data, and disseminates biomedical information--all for the better understanding of molecular processes affecting human health and disease.

links to related research and databases. By following these links, especially the link titled "Database Links," you will be exposed to numerous specialized databases that are largely used by the scientific community. These databases are overly technical and seldom used by the general public, but offer an abundance of information. The following is an example of the results you can obtain from the OMIM for primary immunodeficiency:

- **Acute Promyelocytic Leukemia, Inducer of**  
Web site: <http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispim?102578>
- **Adenosine Deaminase**  
Web site: <http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispim?102700>
- **Agammaglobulinemia, Non-bruton Type**  
Web site: <http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispim?601495>
- **Albinism with Immune and Hematologic Defects**  
Web site: <http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispim?203285>
- **Angiotensin Receptor-like 1**  
Web site: <http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispim?600052>
- **Apelin**  
Web site: <http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispim?300297>
- **Ataxia-telangiectasia**  
Web site: <http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispim?208900>
- **Bare Lymphocyte Syndrome, Type I**  
Web site: <http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispim?604571>
- **Bare Lymphocyte Syndrome, Type II**  
Web site: <http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispim?209920>
- **B-cell CLL/lymphoma 2**  
Web site: <http://www.ncbi.nlm.nih.gov/htbin-post/Omim/dispim?151430>

## Genes and Disease (NCBI - Map)

The Genes and Disease database is produced by the National Center for Biotechnology Information of the National Library of Medicine at the National Institutes of Health. Go to <http://www.ncbi.nlm.nih.gov/disease/>, and browse the system pages to have a full view of important conditions linked to human genes. Since this site is regularly updated, you may wish to re-visit it from time to time. The following systems and associated disorders are addressed:

- **Immune System:** Fights invaders.  
Examples: Asthma, autoimmune polyglandular syndrome, Crohn's disease, DiGeorge syndrome, familial Mediterranean fever, immunodeficiency with Hyper-IgM, severe combined immunodeficiency.  
Web site: <http://www.ncbi.nlm.nih.gov/disease/Immune.html>
- **Metabolism:** Food and energy.  
Examples: Adreno-leukodystrophy, Atherosclerosis, Best disease, Gaucher disease, Glucose galactose malabsorption, Gyrate atrophy, Juvenile onset diabetes, Obesity, Paroxysmal nocturnal hemoglobinuria, Phenylketonuria, Refsum disease, Tangier disease, Tay-Sachs disease.  
Web site: <http://www.ncbi.nlm.nih.gov/disease/Metabolism.html>
- **Nervous System:** Mind and body.  
Examples: Alzheimer disease, Amyotrophic lateral sclerosis, Angelman syndrome, Charcot-Marie-Tooth disease, epilepsy, essential tremor, Fragile X syndrome, Friedreich's ataxia, Huntington disease, Niemann-Pick disease, Parkinson disease, Prader-Willi syndrome, Rett syndrome, Spinocerebellar atrophy, Williams syndrome.  
Web site: <http://www.ncbi.nlm.nih.gov/disease/Brain.html>
- **Signals:** Cellular messages.  
Examples: Ataxia telangiectasia, Baldness, Cockayne syndrome, Glaucoma, SRY: sex determination, Tuberous sclerosis, Waardenburg syndrome, Werner syndrome.  
Web site: <http://www.ncbi.nlm.nih.gov/disease/Signals.html>
- **Transporters:** Pumps and channels.  
Examples: Cystic Fibrosis, deafness, diastrophic dysplasia, Hemophilia A, long-QT syndrome, Menkes syndrome, Pendred syndrome, polycystic kidney disease, sickle cell anemia, Wilson's disease, Zellweger syndrome.  
Web site: <http://www.ncbi.nlm.nih.gov/disease/Transporters.html>

## Entrez

*Entrez* is a search and retrieval system that integrates several linked databases at the National Center for Biotechnology Information (NCBI). These databases include nucleotide sequences, protein sequences, macromolecular structures, whole genomes, and MEDLINE through PubMed. Entrez provides access to the following databases:

- **PubMed:** Biomedical literature (PubMed),  
Web site: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed>
- **Nucleotide Sequence Database (Genbank):**  
Web site:  
<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Nucleotide>
- **Protein Sequence Database:**  
Web site: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Protein>
- **Structure:** Three-dimensional macromolecular structures,  
Web site: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Structure>
- **Genome:** Complete genome assemblies,  
Web site: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Genome>
- **PopSet:** Population study data sets,  
Web site: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Popset>
- **OMIM:** Online Mendelian Inheritance in Man,  
Web site: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM>
- **Taxonomy:** Organisms in GenBank,  
Web site:  
<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Taxonomy>
- **Books:** Online books,  
Web site: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=books>
- **ProbeSet:** Gene Expression Omnibus (GEO),  
Web site: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=geo>
- **3D Domains:** Domains from Entrez Structure,  
Web site: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=geo>
- **NCBI's Protein Sequence Information Survey Results:**  
Web site: <http://www.ncbi.nlm.nih.gov/About/proteinsurvey/>

To access the Entrez system at the National Center for Biotechnology Information, go to <http://www.ncbi.nlm.nih.gov/entrez/>, and then select the database that you would like to search. The databases available are listed in

the drop box next to "Search." In the box next to "for," enter "primary immunodeficiency" (or synonyms) and click "Go."

### **Jablonski's Multiple Congenital Anomaly/Mental Retardation (MCA/MR) Syndromes Database<sup>37</sup>**

This online resource can be quite useful. It has been developed to facilitate the identification and differentiation of syndromic entities. Special attention is given to the type of information that is usually limited or completely omitted in existing reference sources due to space limitations of the printed form.

At [http://www.nlm.nih.gov/mesh/jablonski/syndrome\\_toc/toc\\_a.html](http://www.nlm.nih.gov/mesh/jablonski/syndrome_toc/toc_a.html) you can also search across syndromes using an alphabetical index. You can also search at [http://www.nlm.nih.gov/mesh/jablonski/syndrome\\_db.html](http://www.nlm.nih.gov/mesh/jablonski/syndrome_db.html).

### **The Genome Database<sup>38</sup>**

Established at Johns Hopkins University in Baltimore, Maryland in 1990, the Genome Database (GDB) is the official central repository for genomic mapping data resulting from the Human Genome Initiative. In the spring of 1999, the Bioinformatics Supercomputing Centre (BiSC) at the Hospital for Sick Children in Toronto, Ontario assumed the management of GDB. The Human Genome Initiative is a worldwide research effort focusing on structural analysis of human DNA to determine the location and sequence of the estimated 100,000 human genes. In support of this project, GDB stores and curates data generated by researchers worldwide who are engaged in the mapping effort of the Human Genome Project (HGP). GDB's mission is to provide scientists with an encyclopedia of the human genome which is continually revised and updated to reflect the current state of scientific knowledge. Although GDB has historically focused on gene mapping, its focus will broaden as the Genome Project moves from mapping to sequence, and finally, to functional analysis.

To access the GDB, simply go to the following hyperlink: <http://www.gdb.org/>. Search "All Biological Data" by "Keyword." Type "primary immunodeficiency" (or synonyms) into the search box, and review

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<sup>37</sup> Adapted from the National Library of Medicine:

[http://www.nlm.nih.gov/mesh/jablonski/about\\_syndrome.html](http://www.nlm.nih.gov/mesh/jablonski/about_syndrome.html).

<sup>38</sup> Adapted from the Genome Database:

<http://gdbwww.gdb.org/gdb/aboutGDB.html#mission>.

the results. If more than one word is used in the search box, then separate each one with the word “and” or “or” (using “or” might be useful when using synonyms). This database is extremely technical as it was created for specialists. The articles are the results which are the most accessible to non-professionals and often listed under the heading “Citations.” The contact names are also accessible to non-professionals.

## Specialized References

The following books are specialized references written for professionals interested in primary immunodeficiency (sorted alphabetically by title; hyperlinks provide rankings, information, and reviews at Amazon.com):

- **Atlas of Pediatric Physical Diagnosis** by Basil J. Zitelli, Holly W. Davis (Editor); Hardcover, 3rd edition (March 1997), Mosby-Year Book; ISBN: 0815199309;  
<http://www.amazon.com/exec/obidos/ASIN/0815199309/icongroupinterna>
- **The 5-Minute Pediatric Consult** by M. William Schwartz (Editor); Hardcover - 1050 pages, 2nd edition (January 15, 2000), Lippincott, Williams & Wilkins; ISBN: 0683307444;  
<http://www.amazon.com/exec/obidos/ASIN/0683307444/icongroupinterna>
- **Nelson Textbook of Pediatrics** by Richard E. Behrman (Editor), et al; Hardcover - 2414 pages, 16th edition (January 15, 2000), W B Saunders Co; ISBN: 0721677673;  
<http://www.amazon.com/exec/obidos/ASIN/0721677673/icongroupinterna>



## **PART III. APPENDICES**

### **ABOUT PART III**

Part III is a collection of appendices on general medical topics relating to primary immunodeficiency and related conditions.



## **APPENDIX A. RESEARCHING YOUR CHILD'S MEDICATIONS**

### **Overview**

There are a number of sources available on new or existing medications which could be prescribed to treat primary immunodeficiency. While a number of hard copy or CD-Rom resources are available to parents and physicians for research purposes, a more flexible method is to use Internet-based databases. In this chapter, we will begin with a general overview of medications. We will then proceed to outline official recommendations on how you should view your child's medications. You may also want to research medications that your child is currently taking for other conditions as they may interact with medications for primary immunodeficiency. Research can give you information on the side effects, interactions, and limitations of prescription drugs used in the treatment of primary immunodeficiency. Broadly speaking, there are two sources of information on approved medications: public sources and private sources. We will emphasize free-to-use public sources.

## Your Child's Medications: The Basics<sup>39</sup>

The Agency for Health Care Research and Quality has published extremely useful guidelines on the medication aspects of primary immunodeficiency. Giving your child medication can involve many steps and decisions each day. The AHCQRQ recommends that parents take part in treatment decisions. Do not be afraid to ask questions and talk about your concerns. By taking a moment to ask questions, your child may be spared from possible problems. Here are some points to cover each time a new medicine is prescribed:

- Ask about all parts of your child's treatment, including diet changes, exercise, and medicines.
- Ask about the risks and benefits of each medicine or other treatment your child might receive.
- Ask how often you or your child's doctor will check for side effects from a given medication.

Do not hesitate to tell the doctor about preferences you have for your child's medicines. You may want your child to have a medicine with the fewest side effects, or the fewest doses to take each day. You may care most about cost. Or, you may want the medicine the doctor believes will work the best. Sharing your concerns will help the doctor select the best treatment for your child.

Do not be afraid to "bother" the doctor with your questions about medications for primary immunodeficiency. You can also talk to a nurse or a pharmacist. They can help you better understand your child's treatment plan. Talking over your child's options with someone you trust can help you make better choices. Specifically, ask the doctor the following:

- The name of the medicine and what it is supposed to do.
- How and when to give your child the medicine, how much, and for how long.
- What food, drinks, other medicines, or activities your child should avoid while taking the medicine.
- What side effects your child may experience, and what to do if they occur.
- If there are any refills, and how often.
- About any terms or directions you do not understand.
- What to do if your child misses a dose.

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<sup>39</sup> This section is adapted from AHCQRQ: <http://www.ahcpr.gov/consumer/ncpiebro.htm>.

- If there is written information you can take home (most pharmacies have information sheets on prescription medicines; some even offer large-print or Spanish versions).

Do not forget to tell the doctor about all the medicines your child is currently taking (not just those for primary immunodeficiency). This includes prescription medicines and the medicines that you buy over the counter. When talking to the doctor, you may wish to prepare a list of medicines your child is currently taking including why and in what forms. Be sure to include the following information for each:

- Name of medicine
- Reason taken
- Dosage
- Time(s) of day

Also include any over-the-counter medicines, such as:

- Laxatives
- Diet pills
- Vitamins
- Cold medicine
- Aspirin or other pain, headache, or fever medicine
- Cough medicine
- Allergy relief medicine
- Antacids
- Sleeping pills
- Others (include names)

## **Learning More about Your Child's Medications**

Because of historical investments by various organizations and the emergence of the Internet, it has become rather simple to learn about the medications the doctor has recommended for primary immunodeficiency. One such source is the United States Pharmacopeia. In 1820, eleven physicians met in Washington, D.C. to establish the first compendium of standard drugs for the United States. They called this compendium the "U.S. Pharmacopeia (USP)." Today, the USP is a non-profit organization consisting of 800 volunteer scientists, eleven elected officials, and 400 representatives of

state associations and colleges of medicine and pharmacy. The USP is located in Rockville, Maryland, and its home page is located at **[www.usp.org](http://www.usp.org)**. The USP currently provides standards for over 3,700 medications. The resulting USP DI® Advice for the Patient® can be accessed through the National Library of Medicine of the National Institutes of Health. The database is partially derived from lists of federally approved medications in the Food and Drug Administration's (FDA) Drug Approvals database.<sup>40</sup>

While the FDA database is rather large and difficult to navigate, the Pharmacopeia is both user-friendly and free to use. It covers more than 9,000 prescription and over-the-counter medications. To access this database, simply type the following hyperlink into your Web browser: **<http://www.nlm.nih.gov/medlineplus/druginformation.html>**. To view examples of a given medication (brand names, category, description, preparation, proper use, precautions, side effects, etc.), simply follow the hyperlinks indicated within the United States Pharmacopoeia (USP). It is important to read the disclaimer by the USP (**<http://www.nlm.nih.gov/medlineplus/drugdisclaimer.html>**) before using the information provided.

## Commercial Databases

In addition to the medications listed in the USP above, a number of commercial sites are available by subscription to physicians and their institutions. You may be able to access these sources from your local medical library or your child's doctor's office.

### Reuters Health Drug Database

The Reuters Health Drug Database can be searched by keyword at the hyperlink: **<http://www.reutershealth.com/frame2/drug.html>**. The following medications are listed in the Reuters' database as associated with primary immunodeficiency (including those with contraindications):<sup>41</sup>

- **Azathioprine**  
<http://www.reutershealth.com/atoz/html/Azathioprine.htm>

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<sup>40</sup> Though cumbersome, the FDA database can be freely browsed at the following site: **[www.fda.gov/cder/da/da.htm](http://www.fda.gov/cder/da/da.htm)**.

<sup>41</sup> Adapted from *A to Z Drug Facts* by Facts and Comparisons.

- **Corticotropin**  
<http://www.reutershealth.com/atoz/html/Corticotropin.htm>
- **Corticotropin (Adrenocorticotrophic hormone; ACTH)**  
[http://www.reutershealth.com/atoz/html/Corticotropin\\_\(Adrenocorticotrophic\\_hormone;\\_ACTH\).htm](http://www.reutershealth.com/atoz/html/Corticotropin_(Adrenocorticotrophic_hormone;_ACTH).htm)
- **Cyclosporine**  
<http://www.reutershealth.com/atoz/html/Cyclosporine.htm>
- **Cyclosporine(Cyclosporin A)**  
[http://www.reutershealth.com/atoz/html/Cyclosporine\(Cyclosporin\\_A\).htm](http://www.reutershealth.com/atoz/html/Cyclosporine(Cyclosporin_A).htm)
- **Enalapril Maleate**  
[http://www.reutershealth.com/atoz/html/Enalapril\\_Maleate.htm](http://www.reutershealth.com/atoz/html/Enalapril_Maleate.htm)
- **Fosinopril Sodium**  
[http://www.reutershealth.com/atoz/html/Fosinopril\\_Sodium.htm](http://www.reutershealth.com/atoz/html/Fosinopril_Sodium.htm)
- **Immune Globulin Intravenous**  
[http://www.reutershealth.com/atoz/html/Immune\\_Globulin\\_Intravenous.htm](http://www.reutershealth.com/atoz/html/Immune_Globulin_Intravenous.htm)
- **Immune Globulin Intravenous (IGIV)**  
[http://www.reutershealth.com/atoz/html/Immune\\_Globulin\\_Intravenous\\_\(IGIV\).htm](http://www.reutershealth.com/atoz/html/Immune_Globulin_Intravenous_(IGIV).htm)
- **Immune Globulin IV**  
[http://www.reutershealth.com/atoz/html/Immune\\_Globulin\\_IV.htm](http://www.reutershealth.com/atoz/html/Immune_Globulin_IV.htm)
- **Lisinopril**  
<http://www.reutershealth.com/atoz/html/Lisinopril.htm>
- **Methylprednisolone**  
<http://www.reutershealth.com/atoz/html/Methylprednisolone.htm>
- **Moexipril HCl**  
[http://www.reutershealth.com/atoz/html/Moexipril\\_HCl.htm](http://www.reutershealth.com/atoz/html/Moexipril_HCl.htm)
- **Muromonab&ndash;CD3**  
<http://www.reutershealth.com/atoz/html/Muromonab&ndash;CD3.htm>
- **Mycophenolate Mofetil**  
[http://www.reutershealth.com/atoz/html/Mycophenolate\\_Mofetil.htm](http://www.reutershealth.com/atoz/html/Mycophenolate_Mofetil.htm)
- **Perindopril Erbumine**  
[http://www.reutershealth.com/atoz/html/Perindopril\\_Erbumine.htm](http://www.reutershealth.com/atoz/html/Perindopril_Erbumine.htm)

- **Pneumococcal Vaccine Polyvalent**  
[http://www.reutershealth.com/atoz/html/Pneumococcal\\_Vaccine\\_Polyvalent.htm](http://www.reutershealth.com/atoz/html/Pneumococcal_Vaccine_Polyvalent.htm)
- **Poliovirus Vaccine Live Oral Trivalent**  
[http://www.reutershealth.com/atoz/html/Poliovirus\\_Vaccine\\_Live\\_Oral\\_Trivalent.htm](http://www.reutershealth.com/atoz/html/Poliovirus_Vaccine_Live_Oral_Trivalent.htm)
- **Prednisolone**  
<http://www.reutershealth.com/atoz/html/Prednisolone.htm>
- **Prednisone**  
<http://www.reutershealth.com/atoz/html/Prednisone.htm>
- **Quinapril HCl**  
[http://www.reutershealth.com/atoz/html/Quinapril\\_HCl.htm](http://www.reutershealth.com/atoz/html/Quinapril_HCl.htm)
- **Ramipril**  
<http://www.reutershealth.com/atoz/html/Ramipril.htm>
- **Rifampin**  
<http://www.reutershealth.com/atoz/html/Rifampin.htm>
- **Tetanus and Diphtheria Toxoids**  
[http://www.reutershealth.com/atoz/html/Tetanus\\_and\\_Diphtheria\\_Toxoids.htm](http://www.reutershealth.com/atoz/html/Tetanus_and_Diphtheria_Toxoids.htm)
- **Trandolapril**  
<http://www.reutershealth.com/atoz/html/Trandolapril.htm>
- **Triamcinolone**  
<http://www.reutershealth.com/atoz/html/Triamcinolone.htm>
- **Tuberculin Purified Protein Derivative**  
[http://www.reutershealth.com/atoz/html/Tuberculin\\_Purified\\_Protein\\_Derivative.htm](http://www.reutershealth.com/atoz/html/Tuberculin_Purified_Protein_Derivative.htm)
- **Zidovudine**  
<http://www.reutershealth.com/atoz/html/Zidovudine.htm>

### **Mosby's GenRx**

Mosby's GenRx database (also available on CD-Rom and book format) covers 45,000 drug products including generics and international brands. It provides information on prescribing and drug interactions. Information can be obtained at the following hyperlink:  
<http://www.genrx.com/Mosby/PhyGenRx/group.html>.



## Physicians Desk Reference

The Physicians Desk Reference database (also available in CD-Rom and book format) is a full-text drug database. The database is searchable by brand name, generic name or by indication. It features multiple drug interactions reports. Information can be obtained at the following hyperlink: [http://physician.pdr.net/physician/templates/en/acl/psuser\\_t.htm](http://physician.pdr.net/physician/templates/en/acl/psuser_t.htm).

## Other Web Sites

A number of additional Web sites discuss drug information. As an example, you may like to look at **www.drugs.com** which reproduces the information in the Pharmacopeia as well as commercial information. You may also want to consider the Web site of the Medical Letter, Inc. which allows users to download articles on various drugs and therapeutics for a nominal fee: <http://www.medletter.com/>.

## Contraindications and Interactions (Hidden Dangers)

Some of the medications mentioned in the previous discussions can be problematic for children with primary immunodeficiency--not because they are used in the treatment process, but because of contraindications, or side effects. Medications with contraindications are those that could react with drugs used to treat primary immunodeficiency or potentially create deleterious side effects in patients with primary immunodeficiency. You should ask the physician about any contraindications, especially as these might apply to other medications that your child may be taking for common ailments.

Drug-drug interactions occur when two or more drugs react with each other. This drug-drug interaction may cause your child to experience an unexpected side effect. Drug interactions may make medications less effective, cause unexpected side effects, or increase the action of a particular drug. Some drug interactions can even be harmful to your child.

Be sure to read the label every time you give your child a nonprescription or prescription drug, and take the time to learn about drug interactions. These precautions may be critical to your child's health. You can reduce the risk of potentially harmful drug interactions and side effects with a little bit of knowledge and common sense.

Drug labels contain important information about ingredients, uses, warnings, and directions which you should take the time to read and understand. Labels also include warnings about possible drug interactions. Further, drug labels may change as new information becomes available. This is why it's especially important to read the label every time you give your child a medication. When the doctor prescribes a new drug, discuss all over-the-counter and prescription medications, dietary supplements, vitamins, botanicals, minerals and herbals your child takes. Ask your pharmacist for the package insert for each drug prescribed. The package insert provides more information about potential drug interactions.

## A Final Warning

At some point, you may hear of alternative medications from friends, relatives, or in the news media. Advertisements may suggest that certain alternative drugs can produce positive results for primary immunodeficiency. Exercise caution--some of these drugs may have fraudulent claims, and others may actually hurt your child. The Food and Drug Administration (FDA) is the official U.S. agency charged with discovering which medications are likely to improve the health of patients with primary immunodeficiency. The FDA warns to watch out for<sup>42</sup>:

- Secret formulas (real scientists share what they know)
- Amazing breakthroughs or miracle cures (real breakthroughs don't happen very often; when they do, real scientists do not call them amazing or miracles)
- Quick, painless, or guaranteed cures
- If it sounds too good to be true, it probably isn't true.

If you have any questions about any kind of medical treatment, the FDA may have an office near you. Look for their number in the blue pages of the phone book. You can also contact the FDA through its toll-free number, 1-888-INFO-FDA (1-888-463-6332), or on the World Wide Web at [www.fda.gov](http://www.fda.gov).

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<sup>42</sup> This section has been adapted from  
<http://www.fda.gov/opacom/lowlit/medfraud.html>.

## General References

In addition to the resources provided earlier in this chapter, the following general references describe medications (sorted alphabetically by title; hyperlinks provide rankings, information and reviews at Amazon.com):

- **Complete Guide to Prescription and Nonprescription Drugs 2001 (Complete Guide to Prescription and Nonprescription Drugs, 2001)** by H. Winter Griffith, Paperback 16th edition (2001), Medical Surveillance; ISBN: 0942447417;  
<http://www.amazon.com/exec/obidos/ASIN/039952634X/icongroupinterna>
- **The Essential Guide to Prescription Drugs, 2001** by James J. Rybacki, James W. Long; Paperback - 1274 pages (2001), Harper Resource; ISBN: 0060958162;  
<http://www.amazon.com/exec/obidos/ASIN/0060958162/icongroupinterna>
- **Handbook of Commonly Prescribed Drugs** by G. John Digregorio, Edward J. Barbieri; Paperback 16th edition (2001), Medical Surveillance; ISBN: 0942447417;  
<http://www.amazon.com/exec/obidos/ASIN/0942447417/icongroupinterna>
- **Johns Hopkins Complete Home Encyclopedia of Drugs 2nd ed.** by Simeon Margolis (Ed.), Johns Hopkins; Hardcover - 835 pages (2000), Rebus; ISBN: 0929661583;  
<http://www.amazon.com/exec/obidos/ASIN/0929661583/icongroupinterna>
- **Medical Pocket Reference: Drugs 2002** by Springhouse Paperback 1st edition (2001), Lippincott Williams & Wilkins Publishers; ISBN: 1582550964;  
<http://www.amazon.com/exec/obidos/ASIN/1582550964/icongroupinterna>
- **PDR** by Medical Economics Staff, Medical Economics Staff Hardcover - 3506 pages 55th edition (2000), Medical Economics Company; ISBN: 1563633752;  
<http://www.amazon.com/exec/obidos/ASIN/1563633752/icongroupinterna>
- **Pharmacy Simplified: A Glossary of Terms** by James Grogan; Paperback - 432 pages, 1st edition (2001), Delmar Publishers; ISBN: 0766828581;  
<http://www.amazon.com/exec/obidos/ASIN/0766828581/icongroupinterna>
- **Physician Federal Desk Reference** by Christine B. Fraizer; Paperback 2nd edition (2001), Medicode Inc; ISBN: 1563373971;  
<http://www.amazon.com/exec/obidos/ASIN/1563373971/icongroupinterna>
- **Physician's Desk Reference Supplements** Paperback - 300 pages, 53 edition (1999), ISBN: 1563632950;  
<http://www.amazon.com/exec/obidos/ASIN/1563632950/icongroupinterna>

## Vocabulary Builder

The following vocabulary builder gives definitions of words used in this chapter that have not been defined in previous chapters:

**ACTH:** Adrenocorticotrophic hormone. [EU]

**Lisinopril:** An orally active angiotensin-converting enzyme inhibitor that has been used in the treatment of hypertension and congestive heart failure. [NIH]

**Prednisone:** A synthetic anti-inflammatory glucocorticoid derived from cortisone. It is biologically inert and converted to prednisolone in the liver. [NIH]

**Ramipril:** A long-acting angiotensin-converting enzyme inhibitor. It is a prodrug that is transformed in the liver to its active metabolite ramiprilat. [NIH]

## APPENDIX B. RESEARCHING ALTERNATIVE MEDICINE

### Overview

Complementary and alternative medicine (CAM) is one of the most contentious aspects of modern medical practice. You may have heard of these treatments on the radio or on television. Maybe you have seen articles written about these treatments in magazines, newspapers, or books. Perhaps your child's doctor or your friends have mentioned alternatives.

In this chapter, we will begin by giving you a broad perspective on complementary and alternative therapies. Next, we will introduce you to official information sources on CAM relating to primary immunodeficiency. Finally, at the conclusion of this chapter, we will provide a list of readings on primary immunodeficiency from various authors. We will begin, however, with the National Center for Complementary and Alternative Medicine's (NCCAM) overview of complementary and alternative medicine.

### What Is CAM?<sup>43</sup>

Complementary and alternative medicine (CAM) covers a broad range of healing philosophies, approaches, and therapies. Generally, it is defined as those treatments and healthcare practices which are not taught in medical schools, used in hospitals, or reimbursed by medical insurance companies. Many CAM therapies are termed "holistic," which generally means that the healthcare practitioner considers the whole person, including physical, mental, emotional, and spiritual health. Some of these therapies are also known as "preventive," which means that the practitioner educates and

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<sup>43</sup> Adapted from the NCCAM: <http://nccam.nih.gov/nccam/fcp/faq/index.html#what-is>.

treats the person to prevent health problems from arising, rather than treating symptoms after problems have occurred.

People use CAM treatments and therapies in a variety of ways. Therapies are used alone (often referred to as alternative), in combination with other alternative therapies, or in addition to conventional treatment (sometimes referred to as complementary). Complementary and alternative medicine, or “integrative medicine,” includes a broad range of healing philosophies, approaches, and therapies. Some approaches are consistent with physiological principles of Western medicine, while others constitute healing systems with non-Western origins. While some therapies are far outside the realm of accepted Western medical theory and practice, others are becoming established in mainstream medicine.

Complementary and alternative therapies are used in an effort to prevent illness, reduce stress, prevent or reduce side effects and symptoms, or control or cure disease. Some commonly used methods of complementary or alternative therapy include mind/body control interventions such as visualization and relaxation, manual healing including acupressure and massage, homeopathy, vitamins or herbal products, and acupuncture.

## **What Are the Domains of Alternative Medicine?<sup>44</sup>**

The list of CAM practices changes continually. The reason being is that these new practices and therapies are often proved to be safe and effective, and therefore become generally accepted as “mainstream” healthcare practices. Today, CAM practices may be grouped within five major domains: (1) alternative medical systems, (2) mind-body interventions, (3) biologically-based treatments, (4) manipulative and body-based methods, and (5) energy therapies. The individual systems and treatments comprising these categories are too numerous to list in this sourcebook. Thus, only limited examples are provided within each.

### **Alternative Medical Systems**

Alternative medical systems involve complete systems of theory and practice that have evolved independent of, and often prior to, conventional biomedical approaches. Many are traditional systems of medicine that are

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<sup>44</sup> Adapted from the NCCAM: <http://nccam.nih.gov/nccam/fcp/classify/index.html>.

practiced by individual cultures throughout the world, including a number of venerable Asian approaches.

Traditional oriental medicine emphasizes the balance or disturbances of qi (pronounced chi) or vital energy in health and illness, respectively. Traditional oriental medicine consists of a group of techniques and methods including acupuncture, herbal medicine, oriental massage, and qi gong (a form of energy therapy). Acupuncture involves stimulating specific anatomic points in the body for therapeutic purposes, usually by puncturing the skin with a thin needle.

Ayurveda is India's traditional system of medicine. Ayurvedic medicine (meaning "science of life") is a comprehensive system of medicine that places equal emphasis on body, mind, and spirit. Ayurveda strives to restore the innate harmony of the individual. Some of the primary Ayurvedic treatments include diet, exercise, meditation, herbs, massage, exposure to sunlight, and controlled breathing.

Other traditional healing systems have been developed by the world's indigenous populations. These populations include Native American, Aboriginal, African, Middle Eastern, Tibetan, and Central and South American cultures. Homeopathy and naturopathy are also examples of complete alternative medicine systems.

Homeopathic medicine is an unconventional Western system that is based on the principle that "like cures like," i.e., that the same substance that in large doses produces the symptoms of an illness, in very minute doses cures it. Homeopathic health practitioners believe that the more dilute the remedy, the greater its potency. Therefore, they use small doses of specially prepared plant extracts and minerals to stimulate the body's defense mechanisms and healing processes in order to treat illness.

Naturopathic medicine is based on the theory that a medical condition is the manifestation of alterations in the processes by which the body naturally heals itself and emphasizes health restoration rather than treatment for the condition itself. Naturopathic physicians employ an array of healing practices, including the following: diet and clinical nutrition, homeopathy, acupuncture, herbal medicine, hydrotherapy (the use of water in a range of temperatures and methods of applications), spinal and soft-tissue manipulation, physical therapies (such as those involving electrical currents, ultrasound, and light), therapeutic counseling, and pharmacology.

### **Mind-Body Interventions**

Mind-body interventions employ a variety of techniques designed to facilitate the mind's capacity to affect bodily function and symptoms. Only a select group of mind-body interventions having well-documented theoretical foundations are considered CAM. For example, patient education and cognitive-behavioral approaches are now considered "mainstream." On the other hand, complementary and alternative medicine includes meditation, certain uses of hypnosis, dance, music, and art therapy, as well as prayer and mental healing.

### **Biological-Based Therapies**

This category of CAM includes natural and biological-based practices, interventions, and products, many of which overlap with conventional medicine's use of dietary supplements. This category includes herbal, special dietary, orthomolecular, and individual biological therapies.

Herbal therapy employs an individual herb or a mixture of herbs for healing purposes. An herb is a plant or plant part that produces and contains chemical substances that act upon the body. Special diet therapies, such as those proposed by Drs. Atkins, Ornish, Pritikin, and Weil, are believed to prevent and/or control illness as well as promote health. Orthomolecular therapies aim to treat medical conditions with varying concentrations of chemicals such as magnesium, melatonin, and mega-doses of vitamins. Biological therapies include, for example, the use of laetrile and shark cartilage to treat cancer and the use of bee pollen to treat autoimmune and inflammatory conditions.

### **Manipulative and Body-Based Methods**

This category includes methods that are based on manipulation and/or movement of the body. For example, chiropractors focus on the relationship between structure and function, primarily pertaining to the spine, and how that relationship affects the preservation and restoration of health. Chiropractors use manipulative therapy as an integral treatment tool.

In contrast, osteopaths place particular emphasis on the musculoskeletal system and practice osteopathic manipulation. Osteopaths believe that all of the body's systems work together and that disturbances in one system may



have an impact upon function elsewhere in the body. Massage therapists manipulate the soft tissues of the body to normalize those tissues.

### **Energy Therapies**

Energy therapies focus on energy fields originating within the body (biofields) or those from other sources (electromagnetic fields). Biofield therapies are intended to affect energy fields (the existence of which is not yet experimentally proven) that surround and penetrate the human body. Some forms of energy therapy manipulate biofields by applying pressure and/or manipulating the body by placing the hands in or through these fields. Examples include Qi gong, Reiki and Therapeutic Touch.

Qi gong is a component of traditional oriental medicine that combines movement, meditation, and regulation of breathing to enhance the flow of vital energy (qi) in the body, improve blood circulation, and enhance immune function. Reiki, the Japanese word representing Universal Life Energy, is based on the belief that, by channeling spiritual energy through the practitioner, the spirit is healed and, in turn, heals the physical body. Therapeutic Touch is derived from the ancient technique of “laying-on of hands.” It is based on the premises that the therapist’s healing force affects recovery and that healing is promoted when the body’s energies are in balance. By passing their hands over the patient, these healers identify energy imbalances.

Bioelectromagnetic-based therapies involve the unconventional use of electromagnetic fields to treat illnesses or manage pain. These therapies are often used to treat asthma, cancer, and migraine headaches. Types of electromagnetic fields which are manipulated in these therapies include pulsed fields, magnetic fields, and alternating current or direct current fields.

### **Can Alternatives Affect My Child’s Treatment?**

A critical issue in pursuing complementary alternatives mentioned thus far is the risk that these might have undesirable interactions with your child’s medical treatment. It becomes all the more important to speak with the doctor who can offer advice on the use of alternatives. Official sources confirm this view. Though written for women, we find that the National

Women's Health Information Center's advice on pursuing alternative medicine is appropriate for everyone.<sup>45</sup>

### **Is It Okay to Want Both Traditional and Alternative Medicine?**

Should you wish to explore non-traditional types of treatment, be sure to discuss all issues concerning treatments and therapies with your child's healthcare provider, whether a physician or practitioner of complementary and alternative medicine. Competent healthcare management requires that the practitioner know of all conventional and alternative therapies that your child is taking.

The decision to use complementary and alternative treatments is an important one. Consider before selecting an alternative therapy, the safety and effectiveness of the therapy or treatment, the expertise and qualifications of the healthcare practitioner, and the quality of delivery. These topics should be considered when selecting any practitioner or therapy.

### **Finding CAM References on Primary Immunodeficiency**

Having read the previous discussion, you may be wondering which complementary or alternative treatments might be appropriate for primary immunodeficiency. For the remainder of this chapter, we will direct you to a number of official sources which can assist you in researching studies and publications. Some of these articles are rather technical, so some patience may be required.

#### **National Center for Complementary and Alternative Medicine**

The National Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes of Health (<http://nccam.nih.gov>) has created a link to the National Library of Medicine's databases to allow parents to search for articles that specifically relate to primary immunodeficiency and complementary medicine. To search the database, go to the following Web site: [www.nlm.nih.gov/nccam/camonpubmed.html](http://www.nlm.nih.gov/nccam/camonpubmed.html). Select "CAM on PubMed." Enter "primary immunodeficiency" (or synonyms) into the search box. Click "Go." The following references provide

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<sup>45</sup> Adapted from <http://www.4woman.gov/faq/alternative.htm>.

information on particular aspects of complementary and alternative medicine (CAM) that are related to primary immunodeficiency:

- **"Being dealt with as a whole person." Care seeking and adherence: the benefits of culturally competent care.**  
 Author(s): Schilder AJ, Kennedy C, Goldstone IL, Ogden RD, Hogg RS, O'Shaughnessy MV.  
 Source: Social Science & Medicine (1982). 2001 June; 52(11): 1643-59.  
[http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list\\_uids=11327138&dopt=Abstract](http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11327138&dopt=Abstract)
- **Applying the new concepts of the Neuman Systems Model.**  
 Author(s): Pierce JD, Hutton E.  
 Source: Nursing Forum. 1992 January-March; 27(1): 15-8.  
[http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list\\_uids=1549529&dopt=Abstract](http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1549529&dopt=Abstract)
- **Autogenous vaccine: the best therapy for perianal condyloma acuminata?**  
 Author(s): Wiltz OH, Torregrosa M, Wiltz O.  
 Source: Diseases of the Colon and Rectum. 1995 August; 38(8): 838-41.  
[http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list\\_uids=7634978&dopt=Abstract](http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7634978&dopt=Abstract)
- **Autoimmune blood dyscrasias in five patients with hypogammaglobulinemia: response of neutropenia to vincristine.**  
 Author(s): Webster AD, Platts-Mills TA, Jannossy G, Morgan M, Asherson GL.  
 Source: Journal of Clinical Immunology. 1981 April; 1(2): 113-8.  
[http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list\\_uids=6460784&dopt=Abstract](http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=6460784&dopt=Abstract)
- **Autologous bone marrow transplantation in relapsed HIV-related non-Hodgkin's lymphoma.**  
 Author(s): Gabarre J, Leblond V, Sutton L, Azar N, Jouan M, Boccaccio C, Gonzalez H, Charlotte F, Gentilini M, Binet JL.  
 Source: Bone Marrow Transplantation. 1996 December; 18(6): 1195-7.  
[http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list\\_uids=8971396&dopt=Abstract](http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8971396&dopt=Abstract)
- **Central nervous system involvement in the erythrophagocytic disorders of infancy: the role of cerebrospinal fluid neopterin in their**

**differential diagnosis and clinical management.**

Author(s): Howells DW, Strobel S, Smith I, Levinsky RJ, Hyland K.

Source: Pediatric Research. 1990 August; 28(2): 116-9.

[http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list\\_uids=2395601&dopt=Abstract](http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2395601&dopt=Abstract)

- **Coming out: an overlooked concept.**

Author(s): Saddul RB Jr.

Source: Clinical Nurse Specialist Cns. 1996 January; 10(1): 2-5, 56. Review.

[http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list\\_uids=8705927&dopt=Abstract](http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8705927&dopt=Abstract)

- **Community-based AIDS research.**

Author(s): Merton V.

Source: Evaluation Review. 1990 October; 14(5): 502-37. No Abstract Available.

[http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list\\_uids=11656281&dopt=Abstract](http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11656281&dopt=Abstract)

- **Complementary medicine and HIV infection.**

Author(s): Elion RA, Cohen C.

Source: Primary Care. 1997 December; 24(4): 905-19. Review.

[http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list\\_uids=9386262&dopt=Abstract](http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9386262&dopt=Abstract)

- **Complementary roles for CD19 and Bruton's tyrosine kinase in B lymphocyte signal transduction.**

Author(s): Fujimoto M, Poe JC, Satterthwaite AB, Wahl MI, Witte ON, Tedder TF.

Source: Journal of Immunology (Baltimore, Md. : 1950). 2002 June 1; 168(11): 5465-76.

[http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list\\_uids=12023340&dopt=Abstract](http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12023340&dopt=Abstract)

- **Decreased lymphocytic proliferation by mitogens in patients with transitional cell carcinoma of the renal pelvis subsequent to non-Hodgkin's lymphoma.**

Author(s): Matano S, Nakamura S, Kobayashi K, Misaki T, Matsuda T, Sugimoto T.

Source: American Journal of Hematology. 1996 April; 51(4): 330-2. No Abstract Available.

[http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list\\_uids=8602639&dopt=Abstract](http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8602639&dopt=Abstract)

- **Development and evaluation of a sexual history-taking curriculum for first- and second-year family practice residents.**

Author(s): Ross PE, Landis SE.

Source: Fam Med. 1994 May; 26(5): 293-8.

[http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list\\_uids=8050647&dopt=Abstract](http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8050647&dopt=Abstract)

- **Differential quantification of SIgA and SC by two-directional rocket method.**

Author(s): Kosaka T, Asahina T, Kobayashi N.

Source: Immunology. 1980 August; 40(4): 597-604.

[http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list\\_uids=6776036&dopt=Abstract](http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=6776036&dopt=Abstract)

- **Effect of bone morphogenetic protein-2-expressing muscle-derived cells on healing of critical-sized bone defects in mice.**

Author(s): Lee JY, Musgrave D, Pelinkovic D, Fukushima K, Cummins J, Usas A, Robbins P, Fu FH, Huard J.

Source: The Journal of Bone and Joint Surgery. American Volume. 2001 July; 83-A(7): 1032-9.

[http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list\\_uids=11451972&dopt=Abstract](http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11451972&dopt=Abstract)

- **Efficient transcription and replication of simian immunodeficiency virus in the absence of NF-kappaB and Sp1 binding elements.**

Author(s): Ilyinskii PO, Desrosiers RC.

Source: Journal of Virology. 1996 May; 70(5): 3118-26.

[http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list\\_uids=8627791&dopt=Abstract](http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8627791&dopt=Abstract)

- **Enhanced sensitivity to camptothecin in ataxia-telangiectasia cells and its relationship with the expression of DNA topoisomerase I.**

Author(s): Smith PJ, Makinson TA, Watson JV.

Source: International Journal of Radiation Biology. 1989 February; 55(2): 217-31.

[http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list\\_uids=2563396&dopt=Abstract](http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2563396&dopt=Abstract)

- **Enhancement of interleukin-2 and gamma-interferon production in vitro on cord blood lymphocytes and in vivo on primary cellular immunodeficiency patients with thymic extract (thymostimulin).**

Author(s): Lin CY, Kuo YC, Lin CC, Ou BR.

Source: Journal of Clinical Immunology. 1988 March; 8(2): 103-7.

[http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list\\_uids=3131384&dopt=Abstract](http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3131384&dopt=Abstract)

- **Epstein-Barr virus-associated lymphoma in a child undergoing an autologous stem cell rescue.**

Author(s): Heath JA, Broxson EH Jr, Dole MG, Filippa DA, George D, Lyden D, Dunkel IJ.

Source: Journal of Pediatric Hematology/Oncology : Official Journal of the American Society of Pediatric Hematology/Oncology. 2002 February; 24(2): 160-3.

[http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list\\_uids=11998794&dopt=Abstract](http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11998794&dopt=Abstract)

- **Use of thymosin in the treatment of primary immunodeficiency diseases and cancer.**

Author(s): Goldstein AL, Cohen GH, Rossio JL, Thurman GB, Brown CN, Ulrich JT.

Source: The Medical Clinics of North America. 1976 May; 60(3): 591-606. No Abstract Available.

[http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list\\_uids=131889&dopt=Abstract](http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=131889&dopt=Abstract)

## Additional Web Resources

A number of additional Web sites offer encyclopedic information covering CAM and related topics. The following is a representative sample:

- Alternative Medicine Foundation, Inc.: <http://www.herbmed.org/>
- AOL: <http://search.aol.com/cat.adp?id=169&layer=&from=subcats>
- Chinese Medicine: <http://www.newcenturynutrition.com/>

- drkoop.com®:  
<http://www.drkoop.com/InteractiveMedicine/IndexC.html>
- Family Village: [http://www.familyvillage.wisc.edu/med\\_altn.htm](http://www.familyvillage.wisc.edu/med_altn.htm)
- Google: <http://directory.google.com/Top/Health/Alternative/>
- Healthnotes: <http://www.thedacare.org/healthnotes/>
- Open Directory Project: <http://dmoz.org/Health/Alternative/>
- TPN.com: <http://www.tnp.com/>
- Yahoo.com: [http://dir.yahoo.com/Health/Alternative\\_Medicine/](http://dir.yahoo.com/Health/Alternative_Medicine/)
- WebMD® Health: [http://my.webmd.com/drugs\\_and\\_herbs](http://my.webmd.com/drugs_and_herbs)
- WellNet: <http://www.wellnet.ca/herbsa-c.htm>
- WholeHealthMD.com:  
<http://www.wholehealthmd.com/reflib/0,1529,,00.html>

## General References

A good place to find general background information on CAM is the National Library of Medicine. It has prepared within the MEDLINEplus system an information topic page dedicated to complementary and alternative medicine. To access this page, go to the MEDLINEplus site at: [www.nlm.nih.gov/medlineplus/alternativemedicine.html](http://www.nlm.nih.gov/medlineplus/alternativemedicine.html). This Web site provides a general overview of various topics and can lead to a number of general sources. The following additional references describe, in broad terms, alternative and complementary medicine (sorted alphabetically by title; hyperlinks provide rankings, information, and reviews at Amazon.com):

- **Healthy Child, Whole Child: Integrating the Best of Conventional and Alternative Medicine to Keep Your Kids Healthy** by Stuart H. Ditchek, M.D. and Russell H. Greenfield; Paperback - 464 pages (June 2002), Harper Resource; ISBN: 0062737465;  
<http://www.amazon.com/exec/obidos/ASIN/0062737465/icongroupinterna>
- **Alternative Medicine for Dummies** by James Dillard (Author); Audio Cassette, Abridged edition (1998), Harper Audio; ISBN: 0694520659;  
<http://www.amazon.com/exec/obidos/ASIN/0694520659/icongroupinterna>
- **Complementary and Alternative Medicine Secrets** by W. Kohatsu (Editor); Hardcover (2001), Hanley & Belfus; ISBN: 1560534400;  
<http://www.amazon.com/exec/obidos/ASIN/1560534400/icongroupinterna>

- **Dictionary of Alternative Medicine** by J. C. Segen; Paperback-2nd edition (2001), Appleton & Lange; ISBN: 0838516211;  
<http://www.amazon.com/exec/obidos/ASIN/0838516211/icongroupinterna>
- **Eat, Drink, and Be Healthy: The Harvard Medical School Guide to Healthy Eating** by Walter C. Willett, MD, et al; Hardcover - 352 pages (2001), Simon & Schuster; ISBN: 0684863375;  
<http://www.amazon.com/exec/obidos/ASIN/0684863375/icongroupinterna>
- **Encyclopedia of Natural Medicine, Revised 2nd Edition** by Michael T. Murray, Joseph E. Pizzorno; Paperback - 960 pages, 2nd Rev edition (1997), Prima Publishing; ISBN: 0761511571;  
<http://www.amazon.com/exec/obidos/ASIN/0761511571/icongroupinterna>
- **Integrative Medicine: An Introduction to the Art & Science of Healing** by Andrew Weil (Author); Audio Cassette, Unabridged edition (2001), Sounds True; ISBN: 1564558541;  
<http://www.amazon.com/exec/obidos/ASIN/1564558541/icongroupinterna>
- **New Encyclopedia of Herbs & Their Uses** by Deni Bown; Hardcover - 448 pages, Revised edition (2001), DK Publishing; ISBN: 078948031X;  
<http://www.amazon.com/exec/obidos/ASIN/078948031X/icongroupinterna>
- **Textbook of Complementary and Alternative Medicine** by Wayne B. Jonas; Hardcover (2003), Lippincott, Williams & Wilkins; ISBN: 0683044370;  
<http://www.amazon.com/exec/obidos/ASIN/0683044370/icongroupinterna>

For additional information on complementary and alternative medicine, ask your child's doctor or write to:

National Institutes of Health  
National Center for Complementary and Alternative Medicine  
Clearinghouse  
P. O. Box 8218  
Silver Spring, MD 20907-8218

## Vocabulary Builder

The following vocabulary builder gives definitions of words used in this chapter that have not been defined in previous chapters:

**Amitriptyline:** Tricyclic antidepressant with anticholinergic and sedative properties. It appears to prevent the re-uptake of norepinephrine and serotonin at nerve terminals, thus potentiating the action of these



neurotransmitters. Amitriptyline also appears to antagonize cholinergic and alpha-1 adrenergic responses to bioactive amines. [NIH]

**Carcinoma:** A malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases. [EU]

**Cerebrospinal:** Pertaining to the brain and spinal cord. [EU]

**Condyloma:** *C. acuminatum*; a papilloma with a central core of connective tissue in a treelike structure covered with epithelium, usually occurring on the mucous membrane or skin of the external genitals or in the perianal region. [EU]

**Dyscrasia:** A term formerly used to indicate an abnormal mixture of the four humours; in surviving usages it now is roughly synonymous with 'disease' or 'pathologic condition'. [EU]

**Fluconazole:** Triazole antifungal agent that is used to treat oropharyngeal candidiasis and cryptococcal meningitis in AIDS. [NIH]

**Lymphocytic:** Pertaining to, characterized by, or of the nature of lymphocytes. [EU]

**Morale:** The prevailing temper or spirit of an individual or group in relation to the tasks or functions which are expected. [NIH]

**Neuropathy:** A general term denoting functional disturbances and/or pathological changes in the peripheral nervous system. The etiology may be known e.g. arsenical n., diabetic n., ischemic n., traumatic n.) or unknown. Encephalopathy and myelopathy are corresponding terms relating to involvement of the brain and spinal cord, respectively. The term is also used to designate noninflammatory lesions in the peripheral nervous system, in contrast to inflammatory lesions (neuritis). [EU]

**Neutropenia:** Leukopenia in which the decrease in white blood cells is chiefly in neutrophils. [EU]

**Symptomatic:** 1. pertaining to or of the nature of a symptom. 2. indicative (of a particular disease or disorder). 3. exhibiting the symptoms of a particular disease but having a different cause. 4. directed at the allaying of symptoms, as symptomatic treatment. [EU]

**Tyrosine:** A non-essential amino acid. In animals it is synthesized from phenylalanine. It is also the precursor of epinephrine, thyroid hormones, and melanin. [NIH]



## APPENDIX C. RESEARCHING NUTRITION

### Overview

Since the time of Hippocrates, doctors have understood the importance of diet and nutrition to health and well-being. Since then, they have accumulated an impressive archive of studies and knowledge dedicated to this subject. Based on their experience, doctors and healthcare providers may recommend particular dietary supplements for primary immunodeficiency. Any dietary recommendation is based on age, body mass, gender, lifestyle, eating habits, food preferences, and health condition. It is therefore likely that different patients with primary immunodeficiency may be given different recommendations. Some recommendations may be directly related to primary immunodeficiency, while others may be more related to general health.

In this chapter we will begin by briefly reviewing the essentials of diet and nutrition that will broadly frame more detailed discussions of primary immunodeficiency. We will then show you how to find studies dedicated specifically to nutrition and primary immunodeficiency.

## Food and Nutrition: General Principles

### What Are Essential Foods?

Food is generally viewed by official sources as consisting of six basic elements: (1) fluids, (2) carbohydrates, (3) protein, (4) fats, (5) vitamins, and (6) minerals. Consuming a combination of these elements is considered to be a healthy diet:

- **Fluids** are essential to human life as 80-percent of the body is composed of water. Water is lost via urination, sweating, diarrhea, vomiting, diuretics (drugs that increase urination), caffeine, and physical exertion.
- **Carbohydrates** are the main source for human energy (thermoregulation) and the bulk of typical diets. They are mostly classified as being either simple or complex. Simple carbohydrates include sugars which are often consumed in the form of cookies, candies, or cakes. Complex carbohydrates consist of starches and dietary fibers. Starches are consumed in the form of pastas, breads, potatoes, rice, and other foods. Soluble fibers can be eaten in the form of certain vegetables, fruits, oats, and legumes. Insoluble fibers include brown rice, whole grains, certain fruits, wheat bran and legumes.
- **Proteins** are eaten to build and repair human tissues. Some foods that are high in protein are also high in fat and calories. Food sources for protein include nuts, meat, fish, cheese, and other dairy products.
- **Fats** are consumed for both energy and the absorption of certain vitamins. There are many types of fats, with many general publications recommending the intake of unsaturated fats or those low in cholesterol.

Vitamins and minerals are fundamental to human health, growth, and, in some cases, disease prevention. Most are consumed in your child's diet (exceptions being vitamins K and D which are produced by intestinal bacteria and sunlight on the skin, respectively). Each vitamin and mineral plays a different role in health. The following outlines essential vitamins:

- **Vitamin A** is important to the health of eyes, hair, bones, and skin; sources of vitamin A include foods such as eggs, carrots, and cantaloupe.
- **Vitamin B<sup>1</sup>**, also known as thiamine, is important for the nervous system and energy production; food sources for thiamine include meat, peas, fortified cereals, bread, and whole grains.
- **Vitamin B<sup>2</sup>**, also known as riboflavin, is important for the nervous system and muscles, but is also involved in the release of proteins from

nutrients; food sources for riboflavin include dairy products, leafy vegetables, meat, and eggs.

- **Vitamin B<sup>3</sup>**, also known as niacin, is important for healthy skin and helps the body use energy; food sources for niacin include peas, peanuts, fish, and whole grains
- **Vitamin B<sup>6</sup>**, also known as pyridoxine, is important for the regulation of cells in the nervous system and is vital for blood formation; food sources for pyridoxine include bananas, whole grains, meat, and fish.
- **Vitamin B<sup>12</sup>** is vital for a healthy nervous system and for the growth of red blood cells in bone marrow; food sources for vitamin B<sup>12</sup> include yeast, milk, fish, eggs, and meat.
- **Vitamin C** allows the body's immune system to fight various medical conditions, strengthens body tissue, and improves the body's use of iron; food sources for vitamin C include a wide variety of fruits and vegetables.
- **Vitamin D** helps the body absorb calcium which strengthens bones and teeth; food sources for vitamin D include oily fish and dairy products.
- **Vitamin E** can help protect certain organs and tissues from various degenerative diseases; food sources for vitamin E include margarine, vegetables, eggs, and fish.
- **Vitamin K** is essential for bone formation and blood clotting; common food sources for vitamin K include leafy green vegetables.
- **Folic Acid** maintains healthy cells and blood; food sources for folic acid include nuts, fortified breads, leafy green vegetables, and whole grains.

It should be noted that one can overdose on certain vitamins which become toxic if consumed in excess (e.g. vitamin A, D, E and K).

Like vitamins, minerals are chemicals that are required by the body to remain in good health. Because the human body does not manufacture these chemicals internally, we obtain them from food and other dietary sources. The more important minerals include:

- **Calcium** is needed for healthy bones, teeth, and muscles, but also helps the nervous system function; food sources for calcium include dry beans, peas, eggs, and dairy products.
- **Chromium** is helpful in regulating sugar levels in blood; food sources for chromium include egg yolks, raw sugar, cheese, nuts, beets, whole grains, and meat.

- **Fluoride** is used by the body to help prevent tooth decay and to reinforce bone strength; sources of fluoride include drinking water and certain brands of toothpaste.
- **Iodine** helps regulate the body's use of energy by synthesizing into the hormone thyroxine; food sources include leafy green vegetables, nuts, egg yolks, and red meat.
- **Iron** helps maintain muscles and the formation of red blood cells and certain proteins; food sources for iron include meat, dairy products, eggs, and leafy green vegetables.
- **Magnesium** is important for the production of DNA, as well as for healthy teeth, bones, muscles, and nerves; food sources for magnesium include dried fruit, dark green vegetables, nuts, and seafood.
- **Phosphorous** is used by the body to work with calcium to form bones and teeth; food sources for phosphorous include eggs, meat, cereals, and dairy products.
- **Selenium** primarily helps maintain normal heart and liver functions; food sources for selenium include wholegrain cereals, fish, meat, and dairy products.
- **Zinc** helps wounds heal, the formation of sperm, and encourage rapid growth and energy; food sources include dried beans, shellfish, eggs, and nuts.

The United States government periodically publishes recommended diets and consumption levels of the various elements of food. Again, the doctor may encourage deviations from the average official recommendation based on your child's specific condition. To learn more about basic dietary guidelines, visit the Web site: <http://www.health.gov/dietaryguidelines/>. Based on these guidelines, many foods are required to list the nutrition levels on the food's packaging. Labeling Requirements are listed at the following site maintained by the Food and Drug Administration: <http://www.cfsan.fda.gov/~dms/lab-cons.html>. When interpreting these requirements, the government recommends that consumers become familiar with the following abbreviations before reading FDA literature:<sup>46</sup>

- **DVs (Daily Values):** A new dietary reference term that will appear on the food label. It is made up of two sets of references, DRVs and RDIs.
- **DRVs (Daily Reference Values):** A set of dietary references that applies to fat, saturated fat, cholesterol, carbohydrate, protein, fiber, sodium, and potassium.

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<sup>46</sup> Adapted from the FDA: <http://www.fda.gov/fdac/special/foodlabel/dvs.html>.

- **RDIs (Reference Daily Intakes):** A set of dietary references based on the Recommended Dietary Allowances for essential vitamins and minerals and, in selected groups, protein. The name “RDI” replaces the term “U.S. RDA.”
- **RDAs (Recommended Dietary Allowances):** A set of estimated nutrient allowances established by the National Academy of Sciences. It is updated periodically to reflect current scientific knowledge.

### What Are Dietary Supplements?<sup>47</sup>

Dietary supplements are widely available through many commercial sources, including health food stores, grocery stores, pharmacies, and by mail. Dietary supplements are provided in many forms including tablets, capsules, powders, gel-tabs, extracts, and liquids. Historically in the United States, the most prevalent type of dietary supplement was a multivitamin/mineral tablet or capsule that was available in pharmacies, either by prescription or “over the counter.” Supplements containing strictly herbal preparations were less widely available. Currently in the United States, a wide array of supplement products are available, including vitamin, mineral, other nutrients, and botanical supplements as well as ingredients and extracts of animal and plant origin.

The Office of Dietary Supplements (ODS) of the National Institutes of Health is the official agency of the United States which has the expressed goal of acquiring “new knowledge to help prevent, detect, diagnose, and treat disease and disability, from the rarest genetic disorder to the common cold.”<sup>48</sup> According to the ODS, dietary supplements can have an important impact on the prevention and management of medical conditions and on the maintenance of health.<sup>49</sup> The ODS notes that considerable research on the effects of dietary supplements has been conducted in Asia and Europe where the use of plant products, in particular, has a long tradition. However, the

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<sup>47</sup> This discussion has been adapted from the NIH:  
<http://ods.od.nih.gov/whatare/whatare.html>.

<sup>48</sup> Contact: The Office of Dietary Supplements, National Institutes of Health, Building 31, Room 1B29, 31 Center Drive, MSC 2086, Bethesda, Maryland 20892-2086, Tel: (301) 435-2920, Fax: (301) 480-1845, E-mail: [ods@nih.gov](mailto:ods@nih.gov).

<sup>49</sup> Adapted from <http://ods.od.nih.gov/about/about.html>. The Dietary Supplement Health and Education Act defines dietary supplements as “a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, mineral, amino acid, herb or other botanical; or a dietary substance for use to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent, extract, or combination of any ingredient described above; and intended for ingestion in the form of a capsule, powder, softgel, or gelcap, and not represented as a conventional food or as a sole item of a meal or the diet.”

overwhelming majority of supplements have not been studied scientifically. To explore the role of dietary supplements in the improvement of health care, the ODS plans, organizes, and supports conferences, workshops, and symposia on scientific topics related to dietary supplements. The ODS often works in conjunction with other NIH Institutes and Centers, other government agencies, professional organizations, and public advocacy groups.

To learn more about official information on dietary supplements, visit the ODS site at <http://ods.od.nih.gov/whatare/whatare.html>. Or contact:

The Office of Dietary Supplements  
National Institutes of Health  
Building 31, Room 1B29  
31 Center Drive, MSC 2086  
Bethesda, Maryland 20892-2086  
Tel: (301) 435-2920  
Fax: (301) 480-1845  
E-mail: [ods@nih.gov](mailto:ods@nih.gov)

## Finding Studies on Primary Immunodeficiency

The NIH maintains an office dedicated to nutrition and diet. The National Institutes of Health's Office of Dietary Supplements (ODS) offers a searchable bibliographic database called the IBIDS (International Bibliographic Information on Dietary Supplements). The IBIDS contains over 460,000 scientific citations and summaries about dietary supplements and nutrition as well as references to published international, scientific literature on dietary supplements such as vitamins, minerals, and botanicals.<sup>50</sup> IBIDS is available to the public free of charge through the ODS Internet page: <http://ods.od.nih.gov/databases/ibids.html>.

After entering the search area, you have three choices: (1) IBIDS Consumer Database, (2) Full IBIDS Database, or (3) Peer Reviewed Citations Only. We recommend that you start with the Consumer Database. While you may not find references for the topics that are of most interest to you, check back

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<sup>50</sup> Adapted from <http://ods.od.nih.gov>. IBIDS is produced by the Office of Dietary Supplements (ODS) at the National Institutes of Health to assist the public, healthcare providers, educators, and researchers in locating credible, scientific information on dietary supplements. IBIDS was developed and will be maintained through an interagency partnership with the Food and Nutrition Information Center of the National Agricultural Library, U.S. Department of Agriculture.



periodically as this database is frequently updated. More studies can be found by searching the Full IBIDS Database. Healthcare professionals and researchers generally use the third option, which lists peer-reviewed citations. In all cases, we suggest that you take advantage of the “Advanced Search” option that allows you to retrieve up to 100 fully explained references in a comprehensive format. Type “primary immunodeficiency” (or synonyms) into the search box. To narrow the search, you can also select the “Title” field. The following is a typical result when searching for recently indexed consumer information on primary immunodeficiency:

- **Continued insulin dependence despite normal range insulin sensitivity and insulin connecting peptide levels in a kidney/islet transplant patient.**

Author(s): University of Western Ontario, London, Canada.

Source: Atkison, P R Zucker, P Hramiak, I Paul, T L Dupre, J Behme, M T Scharp, D W Lacy, P E Olack, B J Stiller, C R Diabetes-Care. 1996 March; 19(3): 236-40 0149-5992

- **Hypersensitivity to insulin during remissions in cyclosporin-treated IDDM patients.**

Author(s): Department of Diabetes, Hopital Bichat, Paris, France.

Source: Burcelin, R G Eddouks, M Beylot, M Normand, S Boitard, C Feutren, G Landais, P Riou, J P Girard, J R Bach, J F et al. Diabetes-Care.

## Federal Resources on Nutrition

In addition to the IBIDS, the United States Department of Health and Human Services (HHS) and the United States Department of Agriculture (USDA) provide many sources of information on general nutrition and health. Recommended resources include:

- healthfinder®, HHS's gateway to health information, including diet and nutrition:  
<http://www.healthfinder.gov/scripts/SearchContext.asp?topic=238&page=0>
- The United States Department of Agriculture's Web site dedicated to nutrition information: [www.nutrition.gov](http://www.nutrition.gov)
- The Food and Drug Administration's Web site for federal food safety information: [www.foodsafety.gov](http://www.foodsafety.gov)
- The National Action Plan on Overweight and Obesity sponsored by the United States Surgeon General:  
<http://www.surgeongeneral.gov/topics/obesity/>

- The Center for Food Safety and Applied Nutrition has an Internet site sponsored by the Food and Drug Administration and the Department of Health and Human Services: <http://vm.cfsan.fda.gov/>
- Center for Nutrition Policy and Promotion sponsored by the United States Department of Agriculture: <http://www.usda.gov/cnpp/>
- Food and Nutrition Information Center, National Agricultural Library sponsored by the United States Department of Agriculture: <http://www.nal.usda.gov/fnic/>
- Food and Nutrition Service sponsored by the United States Department of Agriculture: <http://www.fns.usda.gov/fns/>

## Additional Web Resources

A number of additional Web sites offer encyclopedic information covering food and nutrition. The following is a representative sample:

- AOL: <http://search.aol.com/cat.adp?id=174&layer=&from=subcats>
- Family Village: [http://www.familyvillage.wisc.edu/med\\_nutrition.html](http://www.familyvillage.wisc.edu/med_nutrition.html)
- Google: <http://directory.google.com/Top/Health/Nutrition/>
- Healthnotes: <http://www.thedacare.org/healthnotes/>
- Open Directory Project: <http://dmoz.org/Health/Nutrition/>
- Yahoo.com: <http://dir.yahoo.com/Health/Nutrition/>
- WebMD® Health: <http://my.webmd.com/nutrition>
- WholeHealthMD.com:  
<http://www.wholehealthmd.com/reflib/0,1529,,00.html>

## Vocabulary Builder

The following vocabulary builder defines words used in the references in this chapter that have not been defined in previous chapters:

**Carbohydrate:** An aldehyde or ketone derivative of a polyhydric alcohol, particularly of the pentahydric and hexahydric alcohols. They are so named because the hydrogen and oxygen are usually in the proportion to form water, (CH<sub>2</sub>O)<sub>n</sub>. The most important carbohydrates are the starches, sugars, celluloses, and gums. They are classified into mono-, di-, tri-, poly- and heterosaccharides. [EU]

**Cholesterol:** The principal sterol of all higher animals, distributed in body tissues, especially the brain and spinal cord, and in animal fats and oils. [NIH]

**Degenerative:** Undergoing degeneration : tending to degenerate; having the character of or involving degeneration; causing or tending to cause degeneration. [EU]

**Hypersensitivity:** A state of altered reactivity in which the body reacts with an exaggerated immune response to a foreign substance. Hypersensitivity reactions are classified as immediate or delayed, types I and IV, respectively, in the Gell and Coombs classification (q.v.) of immune responses. [EU]

**Iodine:** A nonmetallic element of the halogen group that is represented by the atomic symbol I, atomic number 53, and atomic weight of 126.90. It is a nutritionally essential element, especially important in thyroid hormone synthesis. In solution, it has anti-infective properties and is used topically. [NIH]

**Niacin:** Water-soluble vitamin of the B complex occurring in various animal and plant tissues. Required by the body for the formation of coenzymes NAD and NADP. Has pellagra-curative, vasodilating, and antilipemic properties. [NIH]

**Potassium:** An element that is in the alkali group of metals. It has an atomic symbol K, atomic number 19, and atomic weight 39.10. It is the chief cation in the intracellular fluid of muscle and other cells. Potassium ion is a strong electrolyte and it plays a significant role in the regulation of fluid volume and maintenance of the water-electrolyte balance. [NIH]

**Remission:** A diminution or abatement of the symptoms of a disease; also the period during which such diminution occurs. [EU]

**Riboflavin:** Nutritional factor found in milk, eggs, malted barley, liver, kidney, heart, and leafy vegetables. The richest natural source is yeast. It occurs in the free form only in the retina of the eye, in whey, and in urine; its principal forms in tissues and cells are as FMN and FAD. [NIH]

**Selenium:** An element with the atomic symbol Se, atomic number 34, and atomic weight 78.96. It is an essential micronutrient for mammals and other animals but is toxic in large amounts. Selenium protects intracellular structures against oxidative damage. It is an essential component of glutathione peroxidase. [NIH]

**Thyroxine:** An amino acid of the thyroid gland which exerts a stimulating effect on thyroid metabolism. [NIH]



## APPENDIX D. FINDING MEDICAL LIBRARIES

### Overview

At a medical library you can find medical texts and reference books, consumer health publications, specialty newspapers and magazines, as well as medical journals. In this Appendix, we show you how to quickly find a medical library in your area.

### Preparation

Before going to the library, highlight the references mentioned in this sourcebook that you find interesting. Focus on those items that are not available via the Internet, and ask the reference librarian for help with your search. He or she may know of additional resources that could be helpful to you. Most importantly, your local public library and medical libraries have Interlibrary Loan programs with the National Library of Medicine (NLM), one of the largest medical collections in the world. According to the NLM, most of the literature in the general and historical collections of the National Library of Medicine is available on interlibrary loan to any library. NLM's interlibrary loan services are only available to libraries. If you would like to access NLM medical literature, then visit a library in your area that can request the publications for you.<sup>51</sup>

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<sup>51</sup> Adapted from the NLM: <http://www.nlm.nih.gov/psd/cas/interlibrary.html>.

## Finding a Local Medical Library

The quickest method to locate medical libraries is to use the Internet-based directory published by the National Network of Libraries of Medicine (NN/LM). This network includes 4626 members and affiliates that provide many services to librarians, health professionals, and the public. To find a library in your area, simply visit <http://nnlm.gov/members/adv.html> or call 1-800-338-7657.

## Medical Libraries Open to the Public

In addition to the NN/LM, the National Library of Medicine (NLM) lists a number of libraries that are generally open to the public and have reference facilities. The following is the NLM's list plus hyperlinks to each library Web site. These Web pages can provide information on hours of operation and other restrictions. The list below is a small sample of libraries recommended by the National Library of Medicine (sorted alphabetically by name of the U.S. state or Canadian province where the library is located):<sup>52</sup>

- **Alabama:** Health InfoNet of Jefferson County (Jefferson County Library Cooperative, Lister Hill Library of the Health Sciences), <http://www.uab.edu/infonet/>
- **Alabama:** Richard M. Scrushy Library (American Sports Medicine Institute), <http://www.asmi.org/LIBRARY.HTM>
- **Arizona:** Samaritan Regional Medical Center: The Learning Center (Samaritan Health System, Phoenix, Arizona), <http://www.samaritan.edu/library/bannerlibs.htm>
- **California:** Kris Kelly Health Information Center (St. Joseph Health System), <http://www.humboldt1.com/~kkhic/index.html>
- **California:** Community Health Library of Los Gatos (Community Health Library of Los Gatos), <http://www.healthlib.org/orgresources.html>
- **California:** Consumer Health Program and Services (CHIPS) (County of Los Angeles Public Library, Los Angeles County Harbor-UCLA Medical Center Library) - Carson, CA, <http://www.colapublib.org/services/chips.html>
- **California:** Gateway Health Library (Sutter Gould Medical Foundation)

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<sup>52</sup> Abstracted from <http://www.nlm.nih.gov/medlineplus/libraries.html>.

- **California:** Health Library (Stanford University Medical Center),  
<http://www-med.stanford.edu/healthlibrary/>
- **California:** Patient Education Resource Center - Health Information and Resources (University of California, San Francisco),  
<http://sfghdean.ucsf.edu/barnett/PERC/default.asp>
- **California:** Redwood Health Library (Petaluma Health Care District),  
<http://www.phcd.org/rdwplib.html>
- **California:** San José PlaneTree Health Library,  
<http://planetreesanjose.org/>
- **California:** Sutter Resource Library (Sutter Hospitals Foundation),  
<http://go.sutterhealth.org/comm/resc-library/sac-resources.html>
- **California:** University of California, Davis. Health Sciences Libraries
- **California:** ValleyCare Health Library & Ryan Comer Cancer Resource Center (ValleyCare Health System),  
<http://www.valleycare.com/library.html>
- **California:** Washington Community Health Resource Library (Washington Community Health Resource Library),  
<http://www.healthlibrary.org/>
- **Colorado:** William V. Gervasini Memorial Library (Exempla Healthcare),  
<http://www.exempla.org/conslib.htm>
- **Connecticut:** Hartford Hospital Health Science Libraries (Hartford Hospital), <http://www.harthosp.org/library/>
- **Connecticut:** Healthnet: Connecticut Consumer Health Information Center (University of Connecticut Health Center, Lyman Maynard Stowe Library), <http://library.uchc.edu/departm/hnet/>
- **Connecticut:** Waterbury Hospital Health Center Library (Waterbury Hospital), <http://www.waterburyhospital.com/library/consumer.shtml>
- **Delaware:** Consumer Health Library (Christiana Care Health System, Eugene du Pont Preventive Medicine & Rehabilitation Institute),  
[http://www.christianacare.org/health\\_guide/health\\_guide\\_pmri\\_health\\_info.cfm](http://www.christianacare.org/health_guide/health_guide_pmri_health_info.cfm)
- **Delaware:** Lewis B. Flinn Library (Delaware Academy of Medicine),  
<http://www.delamed.org/chls.html>
- **Georgia:** Family Resource Library (Medical College of Georgia),  
[http://cmc.mcg.edu/kids\\_families/fam\\_resources/fam\\_res\\_lib/frl.htm](http://cmc.mcg.edu/kids_families/fam_resources/fam_res_lib/frl.htm)
- **Georgia:** Health Resource Center (Medical Center of Central Georgia),  
<http://www.mccg.org/hrc/hrchome.asp>

- **Hawaii:** Hawaii Medical Library: Consumer Health Information Service (Hawaii Medical Library), <http://hml.org/CHIS/>
- **Idaho:** DeArmond Consumer Health Library (Kootenai Medical Center), <http://www.nicon.org/DeArmond/index.htm>
- **Illinois:** Health Learning Center of Northwestern Memorial Hospital (Northwestern Memorial Hospital, Health Learning Center), [http://www.nmh.org/health\\_info/hlc.html](http://www.nmh.org/health_info/hlc.html)
- **Illinois:** Medical Library (OSF Saint Francis Medical Center), <http://www.osfsaintfrancis.org/general/library/>
- **Kentucky:** Medical Library - Services for Patients, Families, Students & the Public (Central Baptist Hospital), <http://www.centralbap.com/education/community/library.htm>
- **Kentucky:** University of Kentucky - Health Information Library (University of Kentucky, Chandler Medical Center, Health Information Library), <http://www.mc.uky.edu/PatientEd/>
- **Louisiana:** Alton Ochsner Medical Foundation Library (Alton Ochsner Medical Foundation), <http://www.ochsner.org/library/>
- **Louisiana:** Louisiana State University Health Sciences Center Medical Library-Shreveport, <http://lib-sh.lsuhscc.edu/>
- **Maine:** Franklin Memorial Hospital Medical Library (Franklin Memorial Hospital), <http://www.fchn.org/fmh/lib.htm>
- **Maine:** Gerrish-True Health Sciences Library (Central Maine Medical Center), <http://www.cmmc.org/library/library.html>
- **Maine:** Hadley Parrot Health Science Library (Eastern Maine Healthcare), <http://www.emh.org/hll/hpl/guide.htm>
- **Maine:** Maine Medical Center Library (Maine Medical Center), <http://www.mmc.org/library/>
- **Maine:** Parkview Hospital, <http://www.parkviewhospital.org/communit.htm#Library>
- **Maine:** Southern Maine Medical Center Health Sciences Library (Southern Maine Medical Center), <http://www.smmc.org/services/service.php3?choice=10>
- **Maine:** Stephens Memorial Hospital Health Information Library (Western Maine Health), [http://www.wmhcc.com/hil\\_frame.html](http://www.wmhcc.com/hil_frame.html)
- **Manitoba, Canada:** Consumer & Patient Health Information Service (University of Manitoba Libraries), <http://www.umanitoba.ca/libraries/units/health/reference/chis.html>



- **Manitoba, Canada:** J.W. Crane Memorial Library (Deer Lodge Centre), <http://www.deerlodge.mb.ca/library/libraryservices.shtml>
- **Maryland:** Health Information Center at the Wheaton Regional Library (Montgomery County, Md., Dept. of Public Libraries, Wheaton Regional Library), <http://www.mont.lib.md.us/healthinfo/hic.asp>
- **Massachusetts:** Baystate Medical Center Library (Baystate Health System), <http://www.baystatehealth.com/1024/>
- **Massachusetts:** Boston University Medical Center Alumni Medical Library (Boston University Medical Center), <http://med-libwww.bu.edu/library/lib.html>
- **Massachusetts:** Lowell General Hospital Health Sciences Library (Lowell General Hospital), <http://www.lowellgeneral.org/library/HomePageLinks/WWW.htm>
- **Massachusetts:** Paul E. Woodard Health Sciences Library (New England Baptist Hospital), [http://www.nebh.org/health\\_lib.asp](http://www.nebh.org/health_lib.asp)
- **Massachusetts:** St. Luke's Hospital Health Sciences Library (St. Luke's Hospital), <http://www.southcoast.org/library/>
- **Massachusetts:** Treadwell Library Consumer Health Reference Center (Massachusetts General Hospital), <http://www.mgh.harvard.edu/library/chrcindex.html>
- **Massachusetts:** UMass HealthNet (University of Massachusetts Medical School), <http://healthnet.umassmed.edu/>
- **Michigan:** Botsford General Hospital Library - Consumer Health (Botsford General Hospital, Library & Internet Services), <http://www.botsfordlibrary.org/consumer.htm>
- **Michigan:** Helen DeRoy Medical Library (Providence Hospital and Medical Centers), <http://www.providence-hospital.org/library/>
- **Michigan:** Marquette General Hospital - Consumer Health Library (Marquette General Hospital, Health Information Center), <http://www.mgh.org/center.html>
- **Michigan:** Patient Education Resource Center - University of Michigan Cancer Center (University of Michigan Comprehensive Cancer Center), <http://www.cancer.med.umich.edu/learn/leares.htm>
- **Michigan:** Sladen Library & Center for Health Information Resources - Consumer Health Information, <http://www.sladen.hfhs.org/library/consumer/index.html>

- **Montana:** Center for Health Information (St. Patrick Hospital and Health Sciences Center),  
<http://www.saintpatrick.org/chi/librarydetail.php3?ID=41>
- **National:** Consumer Health Library Directory (Medical Library Association, Consumer and Patient Health Information Section),  
<http://caphis.mlanet.org/directory/index.html>
- **National:** National Network of Libraries of Medicine (National Library of Medicine) - provides library services for health professionals in the United States who do not have access to a medical library,  
<http://nnlm.gov/>
- **National:** NN/LM List of Libraries Serving the Public (National Network of Libraries of Medicine), <http://nnlm.gov/members/>
- **Nevada:** Health Science Library, West Charleston Library (Las Vegas Clark County Library District),  
[http://www.lvcclld.org/special\\_collections/medical/index.htm](http://www.lvcclld.org/special_collections/medical/index.htm)
- **New Hampshire:** Dartmouth Biomedical Libraries (Dartmouth College Library),  
[http://www.dartmouth.edu/~biomed/resources.html#conshealth.html#](http://www.dartmouth.edu/~biomed/resources.html#conshealth.html#/)
- **New Jersey:** Consumer Health Library (Rahway Hospital),  
<http://www.rahwayhospital.com/library.htm>
- **New Jersey:** Dr. Walter Phillips Health Sciences Library (Englewood Hospital and Medical Center),  
<http://www.englewoodhospital.com/links/index.htm>
- **New Jersey:** Meland Foundation (Englewood Hospital and Medical Center), <http://www.geocities.com/ResearchTriangle/9360/>
- **New York:** Choices in Health Information (New York Public Library) - NLM Consumer Pilot Project participant,  
<http://www.nypl.org/branch/health/links.html>
- **New York:** Health Information Center (Upstate Medical University, State University of New York), <http://www.upstate.edu/library/hic/>
- **New York:** Health Sciences Library (Long Island Jewish Medical Center),  
<http://www.lij.edu/library/library.html>
- **New York:** ViaHealth Medical Library (Rochester General Hospital),  
<http://www.nyam.org/library/>
- **Ohio:** Consumer Health Library (Akron General Medical Center, Medical & Consumer Health Library),  
<http://www.akrongeneral.org/hwlibrary.htm>

- **Oklahoma:** Saint Francis Health System Patient/Family Resource Center (Saint Francis Health System), <http://www.sfh-tulsa.com/patientfamilycenter/default.asp>
- **Oregon:** Planetree Health Resource Center (Mid-Columbia Medical Center), <http://www.mcmc.net/phrc/>
- **Pennsylvania:** Community Health Information Library (Milton S. Hershey Medical Center), <http://www.hmc.psu.edu/commhealth/>
- **Pennsylvania:** Community Health Resource Library (Geisinger Medical Center), <http://www.geisinger.edu/education/commmlib.shtml>
- **Pennsylvania:** HealthInfo Library (Moses Taylor Hospital), <http://www.mth.org/healthwellness.html>
- **Pennsylvania:** Hopwood Library (University of Pittsburgh, Health Sciences Library System), <http://www.hsls.pitt.edu/chi/hhrcinfo.html>
- **Pennsylvania:** Koop Community Health Information Center (College of Physicians of Philadelphia), <http://www.collphyphil.org/kooppg1.shtml>
- **Pennsylvania:** Learning Resources Center - Medical Library (Susquehanna Health System), <http://www.shscare.org/services/lrc/index.asp>
- **Pennsylvania:** Medical Library (UPMC Health System), <http://www.upmc.edu/passavant/library.htm>
- **Quebec, Canada:** Medical Library (Montreal General Hospital), <http://ww2.mcgill.ca/mghlib/>
- **South Dakota:** Rapid City Regional Hospital - Health Information Center (Rapid City Regional Hospital, Health Information Center), <http://www.rcrh.org/education/LibraryResourcesConsumers.htm>
- **Texas:** Houston HealthWays (Houston Academy of Medicine-Texas Medical Center Library), <http://hhw.library.tmc.edu/>
- **Texas:** Matustik Family Resource Center (Cook Children's Health Care System), [http://www.cookchildrens.com/Matustik\\_Library.html](http://www.cookchildrens.com/Matustik_Library.html)
- **Washington:** Community Health Library (Kittitas Valley Community Hospital), <http://www.kvch.com/>
- **Washington:** Southwest Washington Medical Center Library (Southwest Washington Medical Center), <http://www.swmedctr.com/Home/>



## APPENDIX E. YOUR CHILD'S RIGHTS AND INSURANCE

### Overview

Parents face a series of issues related more to the healthcare industry than to their children's medical conditions. This appendix covers two important topics in this regard: your responsibilities and your child's rights as a patient, and how to get the most out of your child's medical insurance plan.

### Your Child's Rights as a Patient

The President's Advisory Commission on Consumer Protection and Quality in the Healthcare Industry has created the following summary of your child's rights as a patient.<sup>53</sup>

#### Information Disclosure

Consumers have the right to receive accurate, easily understood information. Some consumers require assistance in making informed decisions about health plans, health professionals, and healthcare facilities. Such information includes:

- **Health plans.** Covered benefits, cost-sharing, and procedures for resolving complaints, licensure, certification, and accreditation status, comparable measures of quality and consumer satisfaction, provider

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<sup>53</sup>Adapted from Consumer Bill of Rights and Responsibilities:  
<http://www.hcqualitycommission.gov/press/cbor.html#head1>.

network composition, the procedures that govern access to specialists and emergency services, and care management information.

- ***Health professionals.*** Education, board certification, and recertification, years of practice, experience performing certain procedures, and comparable measures of quality and consumer satisfaction.
- ***Healthcare facilities.*** Experience in performing certain procedures and services, accreditation status, comparable measures of quality, worker, and consumer satisfaction, and procedures for resolving complaints.
- ***Consumer assistance programs.*** Programs must be carefully structured to promote consumer confidence and to work cooperatively with health plans, providers, payers, and regulators. Desirable characteristics of such programs are sponsorship that ensures accountability to the interests of consumers and stable, adequate funding.

### Choice of Providers and Plans

Consumers have the right to a choice of healthcare providers that is sufficient to ensure access to appropriate high-quality healthcare. To ensure such choice, the Commission recommends the following:

- ***Provider network adequacy.*** All health plan networks should provide access to sufficient numbers and types of providers to assure that all covered services will be accessible without unreasonable delay -- including access to emergency services 24 hours a day and 7 days a week. If a health plan has an insufficient number or type of providers to provide a covered benefit with the appropriate degree of specialization, the plan should ensure that the consumer obtains the benefit outside the network at no greater cost than if the benefit were obtained from participating providers.
- ***Access to specialists.*** Consumers with complex or serious medical conditions who require frequent specialty care should have direct access to a qualified specialist of their choice within a plan's network of providers. Authorizations, when required, should be for an adequate number of direct access visits under an approved treatment plan.
- ***Transitional care.*** Consumers who are undergoing a course of treatment for a chronic or disabling condition at the time they involuntarily change health plans or at a time when a provider is terminated by a plan for other than cause should be able to continue seeing their current specialty providers for up to 90 days to allow for transition of care.

- ***Choice of health plans.*** Public and private group purchasers should, wherever feasible, offer consumers a choice of high-quality health insurance plans.

### **Access to Emergency Services**

Consumers have the right to access emergency healthcare services when and where the need arises. Health plans should provide payment when a consumer presents to an emergency department with acute symptoms of sufficient severity--including severe pain--such that a "prudent layperson" could reasonably expect the absence of medical attention to result in placing that consumer's health in serious jeopardy, serious impairment to bodily functions, or serious dysfunction of any bodily organ or part.

### **Participation in Treatment Decisions**

Consumers have the right and responsibility to fully participate in all decisions related to their healthcare. Consumers who are unable to fully participate in treatment decisions have the right to be represented by parents, guardians, family members, or other conservators. Physicians and other health professionals should:

- Provide parents with sufficient information and opportunity to decide among treatment options consistent with the informed consent process.
- Discuss all treatment options with a parent in a culturally competent manner, including the option of no treatment at all.
- Ensure that persons with disabilities have effective communications with members of the health system in making such decisions.
- Discuss all current treatments a consumer may be undergoing.
- Discuss all risks, benefits, and consequences to treatment or nontreatment.
- Give parents the opportunity to refuse treatment for their children and to express preferences about future treatment decisions.
- Discuss the use of advance directives -- both living wills and durable powers of attorney for healthcare -- with parents.
- Abide by the decisions made by parents consistent with the informed consent process.

Health plans, health providers, and healthcare facilities should:

- Disclose to consumers factors -- such as methods of compensation, ownership of or interest in healthcare facilities, or matters of conscience -- that could influence advice or treatment decisions.
- Assure that provider contracts do not contain any so-called “gag clauses” or other contractual mechanisms that restrict healthcare providers' ability to communicate with and advise parents about medically necessary treatment options for their children.
- Be prohibited from penalizing or seeking retribution against healthcare professionals or other health workers for advocating on behalf of their patients.

### **Respect and Nondiscrimination**

Consumers have the right to considerate, respectful care from all members of the healthcare industry at all times and under all circumstances. An environment of mutual respect is essential to maintain a quality healthcare system. To assure that right, the Commission recommends the following:

- Consumers must not be discriminated against in the delivery of healthcare services consistent with the benefits covered in their policy, or as required by law, based on race, ethnicity, national origin, religion, sex, age, mental or physical disability, sexual orientation, genetic information, or source of payment.
- Consumers eligible for coverage under the terms and conditions of a health plan or program, or as required by law, must not be discriminated against in marketing and enrollment practices based on race, ethnicity, national origin, religion, sex, age, mental or physical disability, sexual orientation, genetic information, or source of payment.

### **Confidentiality of Health Information**

Consumers have the right to communicate with healthcare providers in confidence and to have the confidentiality of their individually identifiable healthcare information protected. Consumers also have the right to review and copy their own medical records and request amendments to their records.



## Complaints and Appeals

Consumers have the right to a fair and efficient process for resolving differences with their health plans, healthcare providers, and the institutions that serve them, including a rigorous system of internal review and an independent system of external review. A free copy of the Patient's Bill of Rights is available from the American Hospital Association.<sup>54</sup>

## Parent Responsibilities

To underscore the importance of finance in modern healthcare as well as your responsibility for the financial aspects of your child's care, the President's Advisory Commission on Consumer Protection and Quality in the Healthcare Industry has proposed that parents understand the following "Consumer Responsibilities."<sup>55</sup> In a healthcare system that protects consumers' rights, it is reasonable to expect and encourage consumers to assume certain responsibilities. Greater involvement by parents in their children's care increases the likelihood of achieving the best outcome and helps support a quality-oriented, cost-conscious environment. Such responsibilities include:

- Take responsibility for maximizing your child's healthy habits.
- Work collaboratively with healthcare providers in developing and carrying out your child's agreed-upon treatment plans.
- Disclose relevant information and clearly communicate wants and needs.
- Use the insurance company's internal complaint and appeal processes to address your concerns.
- Recognize the reality of risks, the limits of the medical science, and the human fallibility of the healthcare professional.
- Be aware of a healthcare provider's obligation to be reasonably efficient and equitable in providing care to the community.
- Become knowledgeable about health plan coverage and options (when available) including all covered benefits, limitations, and exclusions, rules regarding use of network providers, coverage and referral rules,

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<sup>54</sup> To order your free copy of the Patient's Bill of Rights, telephone 312-422-3000 or visit the American Hospital Association's Web site: <http://www.aha.org>. Click on "Resource Center," go to "Search" at bottom of page, and then type in "Patient's Bill of Rights." The Patient's Bill of Rights is also available from Fax on Demand, at 312-422-2020, document number 471124.

<sup>55</sup> Adapted from <http://www.hcqualitycommission.gov/press/cbor.html#head1>.

appropriate processes to secure additional information, and the process to appeal coverage decisions.

- Make a good-faith effort to meet financial obligations.
- Abide by administrative and operational procedures of health plans, healthcare providers, and Government health benefit programs.

## Choosing an Insurance Plan

There are a number of official government agencies that help consumers understand their healthcare insurance choices.<sup>56</sup> The U.S. Department of Labor, in particular, recommends ten ways to make your health benefits choices work best for your family.<sup>57</sup>

**1. Your options are important.** There are many different types of health benefit plans. Find out which one your employer offers, then check out the plan, or plans, offered. Your employer's human resource office, the health plan administrator, or your union can provide information to help you match your family's needs and preferences with the available plans. The more information you have, the better your healthcare decisions will be.

**2. Reviewing the benefits available.** Do the plans offered cover preventive care, well-baby care, vision or dental care? Are there deductibles? Answers to these questions can help determine the out-of-pocket expenses you may face. Cheapest may not always be best. Your goal is high quality health benefits.

**3. Look for quality.** The quality of healthcare services varies, but quality can be measured. You should consider the quality of healthcare in deciding among the healthcare plans or options available to your family. Not all health plans, doctors, hospitals and other providers give the highest quality care. Fortunately, there is quality information you can use right now to help you compare your healthcare choices. Find out how you can measure quality. Consult the U.S. Department of Health and Human Services publication "Your Guide to Choosing Quality Health Care" on the Internet at [www.ahrq.gov/consumer](http://www.ahrq.gov/consumer).

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<sup>56</sup> More information about quality across programs is provided at the following AHRQ Web site:

<http://www.ahrq.gov/consumer/qntascii/qnthplan.htm>.

<sup>57</sup> Adapted from the Department of Labor:

<http://www.dol.gov/dol/pwba/public/pubs/health/top10-text.html>.

**4. Your plan's summary plan description (SPD) provides a wealth of information.** Your health plan administrator can provide you with a copy of your plan's SPD. It outlines your family's benefits and your legal rights under the Employee Retirement Income Security Act (ERISA), the federal law that protects your family's health benefits. It should contain information about the coverage of dependents, what services will require a co-pay, and the circumstances under which your employer can change or terminate a health benefits plan. Save the SPD and all other health plan brochures and documents, along with memos or correspondence from your employer relating to health benefits.

**5. Assess your benefit coverage as your family status changes.** Marriage, divorce, childbirth or adoption, and the death of a spouse are all life events that may signal a need to change your health benefits. You, your spouse and dependent children may be eligible for a special enrollment period under provisions of the Health Insurance Portability and Accountability Act (HIPAA). Even without life-changing events, the information provided by your employer should tell you how you can change benefits or switch plans, if more than one plan is offered. If your spouse's employer also offers a health benefits package, consider coordinating both plans for maximum coverage.

**6. Changing jobs and other life events can affect your family's health benefits.** Under the Consolidated Omnibus Budget Reconciliation Act (COBRA), you, your covered spouse, and your dependent children may be eligible to purchase extended health coverage under your employer's plan if you lose your job, change employers, get divorced, or upon occurrence of certain other events. Coverage can range from 18 to 36 months depending on your situation. COBRA applies to most employers with 20 or more workers and requires your plan to notify you of your rights. Most plans require eligible individuals to make their COBRA election within 60 days of the plan's notice. Be sure to follow up with your plan sponsor if you don't receive notice, and make sure you respond within the allotted time.

**7. HIPAA can also help if you are changing jobs, particularly if you have a medical condition.** HIPAA generally limits pre-existing condition exclusions to a maximum of 12 months (18 months for late enrollees). HIPAA also requires this maximum period to be reduced by the length of time you had prior "creditable coverage." You should receive a certificate documenting your prior creditable coverage from your old plan when coverage ends.

**8. Plan for retirement.** Before you retire, find out what health benefits, if any, extend to you and your spouse during your retirement years. Consult with

your employer's human resources office, your union, the plan administrator, and check your SPD. Make sure there is no conflicting information among these sources about the benefits your family will receive or the circumstances under which they can change or be eliminated. With this information in hand, you can make other important choices, like finding out if you are eligible for Medicare and Medigap insurance coverage.

**9. Know how to file an appeal if a health benefits claim is denied.** Understand how your plan handles grievances and where to make appeals of the plan's decisions. Keep records and copies of correspondence. Check your health benefits package and your SPD to determine who is responsible for handling problems with benefit claims. Contact PWBA for customer service assistance if you are unable to obtain a response to your complaint.

**10. You can take steps to improve the quality of the healthcare and the health benefits your family receives.** Look for and use things like Quality Reports and Accreditation Reports whenever you can. Quality reports may contain consumer ratings -- how satisfied consumers are with the doctors in their plan, for instance-- and clinical performance measures -- how well a healthcare organization prevents and treats illness. Accreditation reports provide information on how accredited organizations meet national standards, and often include clinical performance measures. Look for these quality measures whenever possible. Consult "Your Guide to Choosing Quality Health Care" on the Internet at [www.ahcpr.gov/consumer](http://www.ahcpr.gov/consumer).

## Medicaid

Illness strikes both rich and poor families. For low-income families, Medicaid is available to defer the costs of treatment. In the following pages, you will learn the basics about Medicaid as well as useful contact information on how to find more in-depth information.

Medicaid is a joint federal and state program that helps pay medical costs for some people with low incomes and limited resources. Medicaid programs vary from state to state. You can find more information about Medicaid on the HCFA.gov Web site at <http://www.hcfa.gov/medicaid/medicaid.htm>.

## NORD's Medication Assistance Programs

Finally, the National Organization for Rare Disorders, Inc. (NORD) administers medication programs sponsored by humanitarian-minded pharmaceutical and biotechnology companies to help uninsured or underinsured individuals secure life-saving or life-sustaining drugs.<sup>58</sup> NORD programs ensure that certain vital drugs are available “to those families whose income is too high to qualify for Medicaid but too low to pay for their prescribed medications.” The program has standards for fairness, equity, and unbiased eligibility. It currently covers some 14 programs for nine pharmaceutical companies. NORD also offers early access programs for investigational new drugs (IND) under the approved “Treatment INDs” programs of the Food and Drug Administration (FDA). In these programs, a limited number of individuals can receive investigational drugs that have yet to be approved by the FDA. These programs are generally designed for rare medical conditions. For more information, visit [www.rarediseases.org](http://www.rarediseases.org).

## Additional Resources

In addition to the references already listed in this chapter, you may need more information on health insurance, hospitals, or the healthcare system in general. The NIH has set up an excellent guidance Web site that addresses these and other issues. Topics include:<sup>59</sup>

- Health Insurance:  
<http://www.nlm.nih.gov/medlineplus/healthinsurance.html>
- Health Statistics:  
<http://www.nlm.nih.gov/medlineplus/healthstatistics.html>
- HMO and Managed Care:  
<http://www.nlm.nih.gov/medlineplus/managedcare.html>
- Hospice Care: <http://www.nlm.nih.gov/medlineplus/hospicecare.html>
- Medicaid: <http://www.nlm.nih.gov/medlineplus/medicaid.html>
- Medicare: <http://www.nlm.nih.gov/medlineplus/medicare.html>
- Nursing Homes and Long-term Care:  
<http://www.nlm.nih.gov/medlineplus/nursinghomes.html>

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<sup>58</sup> Adapted from NORD: [http://www.rarediseases.org/cgi-bin/nord/progserv#patient?id=rPIzL9oD&mv\\_pc=30](http://www.rarediseases.org/cgi-bin/nord/progserv#patient?id=rPIzL9oD&mv_pc=30).

<sup>59</sup> You can access this information at:  
<http://www.nlm.nih.gov/medlineplus/healthsystem.html>.

- Patient's Rights, Confidentiality, Informed Consent, Ombudsman Programs, Privacy and Patient Issues:  
**<http://www.nlm.nih.gov/medlineplus/patientissues.html>**
- Veteran's Health, Persian Gulf War, Gulf War Syndrome, Agent Orange:  
**<http://www.nlm.nih.gov/medlineplus/veteranshealth.html>**

## ONLINE GLOSSARIES

The Internet provides access to a number of free-to-use medical dictionaries and glossaries. The National Library of Medicine has compiled the following list of online dictionaries:

- ADAM Medical Encyclopedia (A.D.A.M., Inc.), comprehensive medical reference: **<http://www.nlm.nih.gov/medlineplus/encyclopedia.html>**
- MedicineNet.com Medical Dictionary (MedicineNet, Inc.):  
**<http://www.medterms.com/Script/Main/hp.asp>**
- Merriam-Webster Medical Dictionary (Inteli-Health, Inc.):  
**<http://www.intelihealth.com/IH/>**
- Multilingual Glossary of Technical and Popular Medical Terms in Eight European Languages (European Commission) - Danish, Dutch, English, French, German, Italian, Portuguese, and Spanish:  
**<http://allserv.rug.ac.be/~rvdstich/eugloss/welcome.html>**
- On-line Medical Dictionary (CancerWEB):  
**<http://www.graylab.ac.uk/omd/>**
- Technology Glossary (National Library of Medicine) - Health Care Technology: **<http://www.nlm.nih.gov/nichsr/ta101/ta10108.htm>**
- Terms and Definitions (Office of Rare Diseases):  
**[http://rarediseases.info.nih.gov/ord/glossary\\_a-e.html](http://rarediseases.info.nih.gov/ord/glossary_a-e.html)**

Beyond these, MEDLINEplus contains a very user-friendly encyclopedia covering every aspect of medicine (licensed from A.D.A.M., Inc.). The ADAM Medical Encyclopedia Web site address is **<http://www.nlm.nih.gov/medlineplus/encyclopedia.html>**. ADAM is also available on commercial Web sites such as Web MD (**[http://my.webmd.com/adam/asset/adam\\_disease\\_articles/a\\_to\\_z/a](http://my.webmd.com/adam/asset/adam_disease_articles/a_to_z/a)**) and drkoop.com (**<http://www.drkoop.com/>**). Topics of interest can be researched by using keywords before continuing elsewhere, as these basic definitions and concepts will be useful in more advanced areas of research. You may choose to print various pages specifically relating to primary immunodeficiency and keep them on file.

## Online Dictionary Directories

The following are additional online directories compiled by the National Library of Medicine, including a number of specialized medical dictionaries and glossaries:

- Medical Dictionaries: Medical & Biological (World Health Organization):  
**<http://www.who.int/hlt/virtuallibrary/English/diction.htm#Medical>**
- MEL-Michigan Electronic Library List of Online Health and Medical Dictionaries (Michigan Electronic Library):  
**<http://mel.lib.mi.us/health/health-dictionaries.html>**
- Patient Education: Glossaries (DMOZ Open Directory Project):  
**[http://dmoz.org/Health/Education/Patient\\_Education/Glossaries/](http://dmoz.org/Health/Education/Patient_Education/Glossaries/)**
- Web of Online Dictionaries (Bucknell University):  
**<http://www.yourdictionary.com/diction5.html#medicine>**



## PRIMARY IMMUNODEFICIENCY GLOSSARY

The following is a complete glossary of terms used in this sourcebook. The definitions are derived from official public sources including the National Institutes of Health [NIH] and the European Union [EU]. After this glossary, we list a number of additional hardbound and electronic glossaries and dictionaries that you may wish to consult.

**Abdomen:** That portion of the body that lies between the thorax and the pelvis. [NIH]

**ACTH:** Adrenocorticotrophic hormone. [EU]

**Adenosine:** A nucleoside that is composed of adenine and d-ribose. Adenosine or adenosine derivatives play many important biological roles in addition to being components of DNA and RNA. Adenosine itself is a neurotransmitter. [NIH]

**Adjuvant:** A substance which aids another, such as an auxiliary remedy; in immunology, nonspecific stimulator (e.g., BCG vaccine) of the immune response. [EU]

**Agammaglobulinemia:** An immunologic deficiency state characterized by an extremely low level of generally all classes of gamma-globulin in the blood. [NIH]

**Agonist:** In anatomy, a prime mover. In pharmacology, a drug that has affinity for and stimulates physiologic activity at cell receptors normally stimulated by naturally occurring substances. [EU]

**Albinism:** General term for a number of inherited defects of amino acid metabolism in which there is a deficiency or absence of pigment in the eyes, skin, or hair. [NIH]

**Amitriptyline:** Tricyclic antidepressant with anticholinergic and sedative properties. It appears to prevent the re-uptake of norepinephrine and serotonin at nerve terminals, thus potentiating the action of these neurotransmitters. Amitriptyline also appears to antagonize cholinergic and alpha-1 adrenergic responses to bioactive amines. [NIH]

**Amniocentesis:** Percutaneous transabdominal puncture of the uterus during pregnancy to obtain amniotic fluid. It is commonly used for fetal karyotype determination in order to diagnose abnormal fetal conditions. [NIH]

**Anaphylaxis:** An acute hypersensitivity reaction due to exposure to a previously encountered antigen. The reaction may include rapidly progressing urticaria, respiratory distress, vascular collapse, systemic shock, and death. [NIH]

**Anemia:** A reduction in the number of circulating erythrocytes or in the quantity of hemoglobin. [NIH]

**Anesthesia:** A state characterized by loss of feeling or sensation. This depression of nerve function is usually the result of pharmacologic action and is induced to allow performance of surgery or other painful procedures. [NIH]

**Antibiotic:** A chemical substance produced by a microorganism which has the capacity, in dilute solutions, to inhibit the growth of or to kill other microorganisms. Antibiotics that are sufficiently nontoxic to the host are used as chemotherapeutic agents in the treatment of infectious diseases of man, animals and plants. [EU]

**Antibody:** An immunoglobulin molecule that has a specific amino acid sequence by virtue of which it interacts only with the antigen that induced its synthesis in cells of the lymphoid series (especially plasma cells), or with antigen closely related to it. Antibodies are classified according to their mode of action as agglutinins, bacteriolysins, haemolysins, opsonins, precipitins, etc. [EU]

**Antifungal:** Destructive to fungi, or suppressing their reproduction or growth; effective against fungal infections. [EU]

**Antigen:** Any substance which is capable, under appropriate conditions, of inducing a specific immune response and of reacting with the products of that response, that is, with specific antibody or specifically sensitized T-lymphocytes, or both. Antigens may be soluble substances, such as toxins and foreign proteins, or particulate, such as bacteria and tissue cells; however, only the portion of the protein or polysaccharide molecule known as the antigenic determinant (q.v.) combines with antibody or a specific receptor on a lymphocyte. Abbreviated Ag. [EU]

**Antimicrobial:** Killing microorganisms, or suppressing their multiplication or growth. [EU]

**Aspergillus:** A genus of mitosporic fungi containing about 100 species and eleven different teleomorphs in the family Trichocomaceae. [NIH]

**Ataxia:** Failure of muscular coordination; irregularity of muscular action. [EU]

**Atypical:** Irregular; not conformable to the type; in microbiology, applied specifically to strains of unusual type. [EU]

**Autoimmunity:** Process whereby the immune system reacts against the body's own tissues. Autoimmunity may produce or be caused by autoimmune diseases. [NIH]

**Bacteria:** Unicellular prokaryotic microorganisms which generally possess rigid cell walls, multiply by cell division, and exhibit three principal forms: round or coccid, rodlike or bacillary, and spiral or spirochetal. [NIH]

**Biochemical:** Relating to biochemistry; characterized by, produced by, or involving chemical reactions in living organisms. [EU]

**Biopsy:** The removal and examination, usually microscopic, of tissue from the living body, performed to establish precise diagnosis. [EU]

**Candidiasis:** Infection with a fungus of the genus *Candida*. It is usually a superficial infection of the moist cutaneous areas of the body, and is generally caused by *C. albicans*; it most commonly involves the skin (dermatocandidiasis), oral mucous membranes (thrush, def. 1), respiratory tract (bronchocandidiasis), and vagina (vaginitis). Rarely there is a systemic infection or endocarditis. Called also moniliasis, candidosis, oidiomycosis, and formerly blastodendriosis. [EU]

**Carbohydrate:** An aldehyde or ketone derivative of a polyhydric alcohol, particularly of the pentahydric and hexahydric alcohols. They are so named because the hydrogen and oxygen are usually in the proportion to form water,  $(CH_2O)_n$ . The most important carbohydrates are the starches, sugars, celluloses, and gums. They are classified into mono-, di-, tri-, poly- and heterosaccharides. [EU]

**Carcinoma:** A malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases. [EU]

**Cellulitis:** An acute, diffuse, and suppurative inflammation of loose connective tissue, particularly the deep subcutaneous tissues, and sometimes muscle, which is most commonly seen as a result of infection of a wound, ulcer, or other skin lesions. [NIH]

**Chimera:** An individual that contains cell populations derived from different zygotes. [NIH]

**Cholesterol:** The principal sterol of all higher animals, distributed in body tissues, especially the brain and spinal cord, and in animal fats and oils. [NIH]

**Chromosomal:** Pertaining to chromosomes. [EU]

**Chronic:** Persisting over a long period of time. [EU]

**Cocaine:** An alkaloid ester extracted from the leaves of plants including coca. It is a local anesthetic and vasoconstrictor and is clinically used for that purpose, particularly in the eye, ear, nose, and throat. It also has powerful central nervous system effects similar to the amphetamines and is a drug of abuse. Cocaine, like amphetamines, acts by multiple mechanisms on brain catecholaminergic neurons; the mechanism of its reinforcing effects is thought to involve inhibition of dopamine uptake. [NIH]

**Colitis:** Inflammation of the colon. [EU]

**Colorectal:** Pertaining to or affecting the colon and rectum. [EU]

**Condyloma:** *C. acuminatum*; a papilloma with a central core of connective

tissue in a treelike structure covered with epithelium, usually occurring on the mucous membrane or skin of the external genitals or in the perianal region. [EU]

**Confusion:** Disturbed orientation in regard to time, place, or person, sometimes accompanied by disordered consciousness. [EU]

**Convulsion:** A violent involuntary contraction or series of contractions of the voluntary muscles. [EU]

**Cryptococcus:** A mitosporic Tremellales fungal genus whose species usually have a capsule and do not form pseudomycellium. Teleomorphs include *Filobasidiella* and *Fidobasidium*. [NIH]

**Cryptosporidium:** A genus of coccidian parasites of the family cryptosporidiidae, found in the intestinal epithelium of many vertebrates including humans. [NIH]

**Cyclophosphamide:** Precursor of an alkylating nitrogen mustard antineoplastic and immunosuppressive agent that must be activated in the liver to form the active aldophosphamide. It is used in the treatment of lymphomas, leukemias, etc. Its side effect, alopecia, has been made use of in fleecing sheep. Cyclophosphamide may also cause sterility, birth defects, mutations, and cancer. [NIH]

**Cytokines:** Non-antibody proteins secreted by inflammatory leukocytes and some non-leukocytic cells, that act as intercellular mediators. They differ from classical hormones in that they are produced by a number of tissue or cell types rather than by specialized glands. They generally act locally in a paracrine or autocrine rather than endocrine manner. [NIH]

**Cytomegalovirus:** A genus of the family herpesviridae, subfamily betaherpesvirinae, infecting the salivary glands, liver, spleen, lungs, eyes, and other organs, in which they produce characteristically enlarged cells with intranuclear inclusions. Infection with Cytomegalovirus is also seen as an opportunistic infection in AIDS. [NIH]

**Cytoskeleton:** The network of filaments, tubules, and interconnecting filamentous bridges which give shape, structure, and organization to the cytoplasm. [NIH]

**Degenerative:** Undergoing degeneration : tending to degenerate; having the character of or involving degeneration; causing or tending to cause degeneration. [EU]

**Dermatology:** A medical specialty concerned with the skin, its structure, functions, diseases, and treatment. [NIH]

**Diphtheria:** A localized infection of mucous membranes or skin caused by toxigenic strains of *Corynebacterium diphtheriae*. It is characterized by the presence of a pseudomembrane at the site of infection. Diphtheria toxin,

produced by *C. diphtheriae*, can cause myocarditis, polyneuritis, and other systemic toxic effects. [NIH]

**Dyscrasia:** A term formerly used to indicate an abnormal mixture of the four humours; in surviving usages it now is roughly synonymous with 'disease' or 'pathologic condition'. [EU]

**Eczema:** A pruritic papulovesicular dermatitis occurring as a reaction to many endogenous and exogenous agents, characterized in the acute stage by erythema, edema associated with a serous exudate between the cells of the epidermis (spongiosis) and an inflammatory infiltrate in the dermis, oozing and vesiculation, and crusting and scaling; and in the more chronic stages by lichenification or thickening or both, signs of excoriations, and hyperpigmentation or hypopigmentation or both. Atopic dermatitis is the most common type of dermatitis. Called also eczematous dermatitis. [EU]

**Endocrinology:** A subspecialty of internal medicine concerned with the metabolism, physiology, and disorders of the endocrine system. [NIH]

**Enteritis:** Inflammation of the intestine, applied chiefly to inflammation of the small intestine; see also enterocolitis. [EU]

**Enzyme:** A protein molecule that catalyses chemical reactions of other substances without itself being destroyed or altered upon completion of the reactions. Enzymes are classified according to the recommendations of the Nomenclature Committee of the International Union of Biochemistry. Each enzyme is assigned a recommended name and an Enzyme Commission (EC) number. They are divided into six main groups; oxidoreductases, transferases, hydrolases, lyases, isomerases, and ligases. [EU]

**Epidemic:** Occurring suddenly in numbers clearly in excess of normal expectancy; said especially of infectious diseases but applied also to any disease, injury, or other health-related event occurring in such outbreaks. [EU]

**Esophagitis:** Inflammation, acute or chronic, of the esophagus caused by bacteria, chemicals, or trauma. [NIH]

**Expectorant:** 1. promoting the ejection, by spitting, of mucus or other fluids from the lungs and trachea. 2. an agent that promotes the ejection of mucus or exudate from the lungs, bronchi, and trachea; sometimes extended to all remedies that quiet cough (antitussives). [EU]

**Fibrosis:** The formation of fibrous tissue; fibroid or fibrous degeneration [EU]

**Fluconazole:** Triazole antifungal agent that is used to treat oropharyngeal candidiasis and cryptococcal meningitis in AIDS. [NIH]

**Fungus:** A general term used to denote a group of eukaryotic protists, including mushrooms, yeasts, rusts, moulds, smuts, etc., which are characterized by the absence of chlorophyll and by the presence of a rigid cell wall composed of chitin, mannans, and sometimes cellulose. They are

usually of simple morphological form or show some reversible cellular specialization, such as the formation of pseudoparenchymatous tissue in the fruiting body of a mushroom. The dimorphic fungi grow, according to environmental conditions, as moulds or yeasts. [EU]

**Gastrointestinal:** Pertaining to or communicating with the stomach and intestine, as a gastrointestinal fistula. [EU]

**Giardia:** A genus of flagellate intestinal protozoa parasitic in various vertebrates, including humans. Characteristics include the presence of four pairs of flagella arising from a complicated system of axonemes and cysts that are ellipsoidal to ovoidal in shape. [NIH]

**Giardiasis:** An infection of the small intestine caused by the flagellated protozoan giardia lamblia. It is spread via contaminated food and water and by direct person-to-person contact. [NIH]

**Gluten:** The protein of wheat and other grains which gives to the dough its tough elastic character. [EU]

**Granulocytes:** Leukocytes with abundant granules in the cytoplasm. They are divided into three groups: neutrophils, eosinophils, and basophils. [NIH]

**Haemophilus:** A genus of pasteurellaceae that consists of several species occurring in animals and humans. Its organisms are described as gram-negative, facultatively anaerobic, coccobacillus or rod-shaped, and nonmotile. [NIH]

**Haplotypes:** The genetic constitution of individuals with respect to one member of a pair of allelic genes, or sets of genes that are closely linked and tend to be inherited together such as those of the major histocompatibility complex. [NIH]

**Hematology:** A subspecialty of internal medicine concerned with morphology, physiology, and pathology of the blood and blood-forming tissues. [NIH]

**Herpes:** Any inflammatory skin disease caused by a herpesvirus and characterized by the formation of clusters of small vesicles. When used alone, the term may refer to herpes simplex or to herpes zoster. [EU]

**Homeostasis:** A tendency to stability in the normal body states (internal environment) of the organism. It is achieved by a system of control mechanisms activated by negative feedback; e.g. a high level of carbon dioxide in extracellular fluid triggers increased pulmonary ventilation, which in turn causes a decrease in carbon dioxide concentration. [EU]

**Humoral:** Of, relating to, proceeding from, or involving a bodily humour - now often used of endocrine factors as opposed to neural or somatic. [EU]

**Hybridization:** The genetic process of crossbreeding to produce a hybrid. Hybrid nucleic acids can be formed by nucleic acid hybridization of DNA

and RNA molecules. Protein hybridization allows for hybrid proteins to be formed from polypeptide chains. [NIH]

**Hyperplasia:** The abnormal multiplication or increase in the number of normal cells in normal arrangement in a tissue. [EU]

**Hypersensitivity:** A state of altered reactivity in which the body reacts with an exaggerated immune response to a foreign substance. Hypersensitivity reactions are classified as immediate or delayed, types I and IV, respectively, in the Gell and Coombs classification (q.v.) of immune responses. [EU]

**Hypoplasia:** Incomplete development or underdevelopment of an organ or tissue. [EU]

**Hypoxia:** Reduction of oxygen supply to tissue below physiological levels despite adequate perfusion of the tissue by blood. [EU]

**Ibuprofen:** A nonsteroidal anti-inflammatory agent with analgesic properties used in the therapy of rheumatism and arthritis. [NIH]

**Iloprost:** An eicosanoid, derived from the cyclooxygenase pathway of arachidonic acid metabolism. It is a stable and synthetic analog of epoprostenol, but with a longer half-life than the parent compound. Its actions are similar to prostacyclin. Iloprost produces vasodilation and inhibits platelet aggregation. [NIH]

**Immunity:** The condition of being immune; the protection against infectious disease conferred either by the immune response generated by immunization or previous infection or by other nonimmunologic factors (innate i.). [EU]

**Inflammation:** A pathological process characterized by injury or destruction of tissues caused by a variety of cytologic and chemical reactions. It is usually manifested by typical signs of pain, heat, redness, swelling, and loss of function. [NIH]

**Influenza:** An acute viral infection involving the respiratory tract. It is marked by inflammation of the nasal mucosa, the pharynx, and conjunctiva, and by headache and severe, often generalized, myalgia. [NIH]

**Infusion:** The therapeutic introduction of a fluid other than blood, as saline solution, solution, into a vein. [EU]

**Insulin:** A protein hormone secreted by beta cells of the pancreas. Insulin plays a major role in the regulation of glucose metabolism, generally promoting the cellular utilization of glucose. It is also an important regulator of protein and lipid metabolism. Insulin is used as a drug to control insulin-dependent diabetes mellitus. [NIH]

**Intestines:** The section of the alimentary canal from the stomach to the anus. It includes the large intestine and small intestine. [NIH]

**Iodine:** A nonmetallic element of the halogen group that is represented by the atomic symbol I, atomic number 53, and atomic weight of 126.90. It is a nutritionally essential element, especially important in thyroid hormone synthesis. In solution, it has anti-infective properties and is used topically. [NIH]

**Jaundice:** A clinical manifestation of hyperbilirubinemia, consisting of deposition of bile pigments in the skin, resulting in a yellowish staining of the skin and mucous membranes. [NIH]

**Lesion:** Any pathological or traumatic discontinuity of tissue or loss of function of a part. [EU]

**Lisinopril:** An orally active angiotensin-converting enzyme inhibitor that has been used in the treatment of hypertension and congestive heart failure. [NIH]

**Lobe:** A more or less well-defined portion of any organ, especially of the brain, lungs, and glands. Lobes are demarcated by fissures, sulci, connective tissue, and by their shape. [EU]

**Lupus:** A form of cutaneous tuberculosis. It is seen predominantly in women and typically involves the nasal, buccal, and conjunctival mucosa. [NIH]

**Lymphocytic:** Pertaining to, characterized by, or of the nature of lymphocytes. [EU]

**Lymphoma:** Any neoplastic disorder of the lymphoid tissue, the term lymphoma often is used alone to denote malignant lymphoma. [EU]

**Malabsorption:** Impaired intestinal absorption of nutrients. [EU]

**Malformation:** A morphologic defect resulting from an intrinsically abnormal developmental process. [EU]

**Malignant:** Tending to become progressively worse and to result in death. Having the properties of anaplasia, invasion, and metastasis; said of tumours. [EU]

**Manifest:** Being the part or aspect of a phenomenon that is directly observable : concretely expressed in behaviour. [EU]

**Meiosis:** A special method of cell division, occurring in maturation of the germ cells, by means of which each daughter nucleus receives half the number of chromosomes characteristic of the somatic cells of the species. [NIH]

**Melanocytes:** Epidermal dendritic pigment cells which control long-term morphological color changes by alteration in their number or in the amount of pigment they produce and store in the pigment containing organelles called melanosomes. Melanophores are larger cells which do not exist in mammals. [NIH]

**Melanoma:** A tumour arising from the melanocytic system of the skin and



other organs. When used alone the term refers to malignant melanoma. [EU]

**Membrane:** A thin layer of tissue which covers a surface, lines a cavity or divides a space or organ. [EU]

**Meningitis:** Inflammation of the meninges. When it affects the dura mater, the disease is termed pachymeningitis; when the arachnoid and pia mater are involved, it is called leptomeningitis, or meningitis proper. [EU]

**Methotrexate:** An antineoplastic antimetabolite with immunosuppressant properties. It is an inhibitor of dihydrofolate reductase and prevents the formation of tetrahydrofolate, necessary for synthesis of thymidylate, an essential component of DNA. [NIH]

**Mobilization:** The process of making a fixed part or stored substance mobile, as by separating a part from surrounding structures to make it accessible for an operative procedure or by causing release into the circulation for body use of a substance stored in the body. [EU]

**Monocytes:** Large, phagocytic mononuclear leukocytes produced in the vertebrate bone marrow and released into the blood; contain a large, oval or somewhat indented nucleus surrounded by voluminous cytoplasm and numerous organelles. [NIH]

**Mononucleosis:** The presence of an abnormally large number of mononuclear leucocytes (monocytes) in the blood. The term is often used alone to refer to infectious mononucleosis. [EU]

**Mucus:** The free slime of the mucous membranes, composed of secretion of the glands, along with various inorganic salts, desquamated cells, and leucocytes. [EU]

**Mycoplasma:** A genus of gram-negative, facultatively anaerobic bacteria bounded by a plasma membrane only. Its organisms are parasites and pathogens, found on the mucous membranes of humans, animals, and birds. [NIH]

**Neonatal:** Pertaining to the first four weeks after birth. [EU]

**Neurologic:** Pertaining to neurology or to the nervous system. [EU]

**Neuropathy:** A general term denoting functional disturbances and/or pathological changes in the peripheral nervous system. The etiology may be known e.g. arsenical n., diabetic n., ischemic n., traumatic n.) or unknown. Encephalopathy and myelopathy are corresponding terms relating to involvement of the brain and spinal cord, respectively. The term is also used to designate noninflammatory lesions in the peripheral nervous system, in contrast to inflammatory lesions (neuritis). [EU]

**Neutropenia:** Leukopenia in which the decrease in white blood cells is chiefly in neutrophils. [EU]

**Neutrophil:** Having an affinity for neutral dyes. [EU]

**Niacin:** Water-soluble vitamin of the B complex occurring in various animal and plant tissues. Required by the body for the formation of coenzymes NAD and NADP. Has pellagra-curative, vasodilating, and antilipemic properties. [NIH]

**Nystagmus:** An involuntary, rapid, rhythmic movement of the eyeball, which may be horizontal, vertical, rotatory, or mixed, i.e., of two varieties. [EU]

**Oocytes:** Female germ cells in stages between the prophase of the first maturation division and the completion of the second maturation division. [NIH]

**Oogenesis:** The formation, development, and maturation of the female germ cell. [NIH]

**Oral:** Pertaining to the mouth, taken through or applied in the mouth, as an oral medication or an oral thermometer. [EU]

**Osteomyelitis:** Inflammation of bone caused by a pyogenic organism. It may remain localized or may spread through the bone to involve the marrow, cortex, cancellous tissue, and periosteum. [EU]

**Overdose:** 1. to administer an excessive dose. 2. an excessive dose. [EU]

**Pancreas:** A mixed exocrine and endocrine gland situated transversely across the posterior abdominal wall in the epigastric and hypochondriac regions. The endocrine portion is comprised of the islets of langerhans, while the exocrine portion is a compound acinar gland that secretes digestive enzymes. [NIH]

**Paralysis:** Loss or impairment of motor function in a part due to lesion of the neural or muscular mechanism; also by analogy, impairment of sensory function (sensory paralysis). In addition to the types named below, paralysis is further distinguished as traumatic, syphilitic, toxic, etc., according to its cause; or as obturator, ulnar, etc., according to the nerve part, or muscle specially affected. [EU]

**Parathyroid:** 1. situated beside the thyroid gland. 2. one of the parathyroid glands. 3. a sterile preparation of the water-soluble principle(s) of the parathyroid glands, administered parenterally as an antihypocalcaemic, especially in the treatment of acute hypoparathyroidism with tetany. [EU]

**Penicillamine:** 3-Mercapto-D-valine. The most characteristic degradation product of the penicillin antibiotics. It is used as an antirheumatic and as a chelating agent in Wilson's disease. [NIH]

**Pharmacokinetics:** The action of drugs in the body over a period of time, including the processes of absorption, distribution, localization in tissues, biotransformation, and excretion. [EU]

**Pharyngitis:** Inflammation of the pharynx. [EU]

**Phenotype:** The outward appearance of the individual. It is the product of interactions between genes and between the genotype and the environment. This includes the killer phenotype, characteristic of yeasts. [NIH]

**Phosphorylase:** An enzyme of the transferase class that catalyzes the phosphorylysis of a terminal alpha-1,4-glycosidic bond at the non-reducing end of a glycogen molecule, releasing a glucose 1-phosphate residue. Phosphorylase should be qualified by the natural substance acted upon. EC 2.4.1.1. [NIH]

**Placenta:** A highly vascular fetal organ through which the fetus absorbs oxygen and other nutrients and excretes carbon dioxide and other wastes. It begins to form about the eighth day of gestation when the blastocyst adheres to the decidua. [NIH]

**Poisoning:** A condition or physical state produced by the ingestion, injection or inhalation of, or exposure to a deleterious agent. [NIH]

**Polyethylene:** A vinyl polymer made from ethylene. It can be branched or linear. Branched or low-density polyethylene is tough and pliable but not to the same degree as linear polyethylene. Linear or high-density polyethylene has a greater hardness and tensile strength. Polyethylene is used in a variety of products, including implants and prostheses. [NIH]

**Postural:** Pertaining to posture or position. [EU]

**Potassium:** An element that is in the alkali group of metals. It has an atomic symbol K, atomic number 19, and atomic weight 39.10. It is the chief cation in the intracellular fluid of muscle and other cells. Potassium ion is a strong electrolyte and it plays a significant role in the regulation of fluid volume and maintenance of the water-electrolyte balance. [NIH]

**Preclinical:** Before a disease becomes clinically recognizable. [EU]

**Predisposition:** A latent susceptibility to disease which may be activated under certain conditions, as by stress. [EU]

**Prednisone:** A synthetic anti-inflammatory glucocorticoid derived from cortisone. It is biologically inert and converted to prednisolone in the liver. [NIH]

**Prenatal:** Existing or occurring before birth, with reference to the fetus. [EU]

**Prostate:** A gland in males that surrounds the neck of the bladder and the urethra. It secretes a substance that liquifies coagulated semen. It is situated in the pelvic cavity behind the lower part of the pubic symphysis, above the deep layer of the triangular ligament, and rests upon the rectum. [NIH]

**Proteins:** Polymers of amino acids linked by peptide bonds. The specific sequence of amino acids determines the shape and function of the protein. [NIH]

**Pyrazinamide:** A pyrazine that is used therapeutically as an antitubercular

agent. [NIH]

**Radiology:** A specialty concerned with the use of x-ray and other forms of radiant energy in the diagnosis and treatment of disease. [NIH]

**Ramipril:** A long-acting angiotensin-converting enzyme inhibitor. It is a prodrug that is transformed in the liver to its active metabolite ramiprilat. [NIH]

**Receptor:** 1. a molecular structure within a cell or on the surface characterized by (1) selective binding of a specific substance and (2) a specific physiologic effect that accompanies the binding, e.g., cell-surface receptors for peptide hormones, neurotransmitters, antigens, complement fragments, and immunoglobulins and cytoplasmic receptors for steroid hormones. 2. a sensory nerve terminal that responds to stimuli of various kinds. [EU]

**Reconstitution:** 1. a type of regeneration in which a new organ forms by the rearrangement of tissues rather than from new formation at an injured surface. 2. the restoration to original form of a substance previously altered for preservation and storage, as the restoration to a liquid state of blood serum or plasma that has been dried and stored. [EU]

**Registries:** The systems and processes involved in the establishment, support, management, and operation of registers, e.g., disease registers. [NIH]

**Remission:** A diminution or abatement of the symptoms of a disease; also the period during which such diminution occurs. [EU]

**Riboflavin:** Nutritional factor found in milk, eggs, malted barley, liver, kidney, heart, and leafy vegetables. The richest natural source is yeast. It occurs in the free form only in the retina of the eye, in whey, and in urine; its principal forms in tissues and cells are as FMN and FAD. [NIH]

**Rifabutin:** A broad-spectrum antibiotic that is being used as prophylaxis against disseminated Mycobacterium avium complex infection in HIV-positive patients. [NIH]

**Rubella:** An acute, usually benign, infectious disease caused by a togavirus and most often affecting children and nonimmune young adults, in which the virus enters the respiratory tract via droplet nuclei and spreads to the lymphatic system. It is characterized by a slight cold, sore throat, and fever, followed by enlargement of the postauricular, suboccipital, and cervical lymph nodes, and the appearances of a fine pink rash that begins on the head and spreads to become generalized. Called also German measles, roetln, röteln, and three-day measles, and rubeola in French and Spanish. [EU]

**Saliva:** The clear, viscous fluid secreted by the salivary glands and mucous glands of the mouth. It contains mucins, water, organic salts, and ptylin. [NIH]

**Sarcoma:** A tumour made up of a substance like the embryonic connective

tissue; tissue composed of closely packed cells embedded in a fibrillar or homogeneous substance. Sarcomas are often highly malignant. [EU]

**Sclerosis:** A induration, or hardening; especially hardening of a part from inflammation and in diseases of the interstitial substance. The term is used chiefly for such a hardening of the nervous system due to hyperplasia of the connective tissue or to designate hardening of the blood vessels. [EU]

**Secretion:** 1. the process of elaborating a specific product as a result of the activity of a gland; this activity may range from separating a specific substance of the blood to the elaboration of a new chemical substance. 2. any substance produced by secretion. [EU]

**Seizures:** Clinical or subclinical disturbances of cortical function due to a sudden, abnormal, excessive, and disorganized discharge of brain cells. Clinical manifestations include abnormal motor, sensory and psychic phenomena. Recurrent seizures are usually referred to as epilepsy or "seizure disorder." [NIH]

**Selenium:** An element with the atomic symbol Se, atomic number 34, and atomic weight 78.96. It is an essential micronutrient for mammals and other animals but is toxic in large amounts. Selenium protects intracellular structures against oxidative damage. It is an essential component of glutathione peroxidase. [NIH]

**Serum:** The clear portion of any body fluid; the clear fluid moistening serous membranes. 2. blood serum; the clear liquid that separates from blood on clotting. 3. immune serum; blood serum from an immunized animal used for passive immunization; an antiserum; antitoxin, or antivenin. [EU]

**Sinusitis:** Inflammation of a sinus. The condition may be purulent or nonpurulent, acute or chronic. Depending on the site of involvement it is known as ethmoid, frontal, maxillary, or sphenoid sinusitis. [EU]

**Solvent:** 1. dissolving; effecting a solution. 2. a liquid that dissolves or that is capable of dissolving; the component of a solution that is present in greater amount. [EU]

**Spectrum:** A charted band of wavelengths of electromagnetic vibrations obtained by refraction and diffraction. By extension, a measurable range of activity, such as the range of bacteria affected by an antibiotic (antibacterial s.) or the complete range of manifestations of a disease. [EU]

**Sputum:** Matter ejected from the lungs, bronchi, and trachea, through the mouth. [EU]

**Staphylococcus:** A genus of gram-positive, facultatively anaerobic, coccoid bacteria. Its organisms occur singly, in pairs, and in tetrads and characteristically divide in more than one plane to form irregular clusters. Natural populations of Staphylococcus are membranes of warm-blooded

animals. Some species are opportunistic pathogens of humans and animals. [NIH]

**Streptococcus:** A genus of gram-positive, coccoid bacteria whose organisms occur in pairs or chains. No endospores are produced. Many species exist as commensals or parasites on man or animals with some being highly pathogenic. A few species are saprophytes and occur in the natural environment. [NIH]

**Symptomatic:** 1. pertaining to or of the nature of a symptom. 2. indicative (of a particular disease or disorder). 3. exhibiting the symptoms of a particular disease but having a different cause. 4. directed at the allaying of symptoms, as symptomatic treatment. [EU]

**Tears:** The fluid secreted by the lacrimal glands. This fluid moistens the conjunctiva and cornea. [NIH]

**Tetanus:** A disease caused by tetanospasmin, a powerful protein toxin produced by clostridium tetani. Tetanus usually occurs after an acute injury, such as a puncture wound or laceration. Generalized tetanus, the most common form, is characterized by tetanic muscular contractions and hyperreflexia. Localized tetanus presents itself as a mild condition with manifestations restricted to muscles near the wound. It may progress to the generalized form. [NIH]

**Thymosin:** Thymosin. A family of heat-stable, polypeptide hormones secreted by the thymus gland. Their biological activities include lymphocytopoiesis, restoration of immunological competence and enhancement of expression of T-cell characteristics and function. They have therapeutic potential in patients having primary or secondary immunodeficiency diseases, cancer or diseases related to aging. [NIH]

**Thyroxine:** An amino acid of the thyroid gland which exerts a stimulating effect on thyroid metabolism. [NIH]

**Toxin:** A poison; frequently used to refer specifically to a protein produced by some higher plants, certain animals, and pathogenic bacteria, which is highly toxic for other living organisms. Such substances are differentiated from the simple chemical poisons and the vegetable alkaloids by their high molecular weight and antigenicity. [EU]

**Toxoplasmosis:** An acute or chronic, widespread disease of animals and humans caused by the obligate intracellular protozoon *Toxoplasma gondii*, transmitted by oocysts containing the pathogen in the feces of cats (the definitive host), usually by contaminated soil, direct exposure to infected feces, tissue cysts in infected meat, or tachyzoites (proliferating forms) in blood. [EU]

**Transfusion:** The introduction of whole blood or blood component directly into the blood stream. [EU]

**Transplantation:** The grafting of tissues taken from the patient's own body or from another. [EU]

**Tuberculosis:** Any of the infectious diseases of man and other animals caused by species of mycobacterium. [NIH]

**Tyrosine:** A non-essential amino acid. In animals it is synthesized from phenylalanine. It is also the precursor of epinephrine, thyroid hormones, and melanin. [NIH]

**Uterus:** The hollow muscular organ in female mammals in which the fertilized ovum normally becomes embedded and in which the developing embryo and fetus is nourished. In the nongravid human, it is a pear-shaped structure; about 3 inches in length, consisting of a body, fundus, isthmus, and cervix. Its cavity opens into the vagina below, and into the uterine tube on either side at the cornu. It is supported by direct attachment to the vagina and by indirect attachment to various other nearby pelvic structures. Called also metra. [EU]

**Vaccine:** A suspension of attenuated or killed microorganisms (bacteria, viruses, or rickettsiae), administered for the prevention, amelioration or treatment of infectious diseases. [EU]

**Varicella:** Chicken pox. [EU]

**Vascular:** Pertaining to blood vessels or indicative of a copious blood supply. [EU]

**Viruses:** Minute infectious agents whose genomes are composed of DNA or RNA, but not both. They are characterized by a lack of independent metabolism and the inability to replicate outside living host cells. [NIH]

**Withdrawal:** 1. a pathological retreat from interpersonal contact and social involvement, as may occur in schizophrenia, depression, or schizoid avoidant and schizotypal personality disorders. 2. (DSM III-R) a substance-specific organic brain syndrome that follows the cessation of use or reduction in intake of a psychoactive substance that had been regularly used to induce a state of intoxication. [EU]

**Xenopus:** An aquatic genus of the family, Pipidae, occurring in Africa and distinguished by having black horny claws on three inner hind toes. [NIH]

**Yeasts:** A general term for single-celled rounded fungi that reproduce by budding. Brewers' and bakers' yeasts are *saccharomyces cerevisiae*; therapeutic dried yeast is yeast, dried. [NIH]

## General Dictionaries and Glossaries

While the above glossary is essentially complete, the dictionaries listed here cover virtually all aspects of medicine, from basic words and phrases to more advanced terms (sorted alphabetically by title; hyperlinks provide rankings, information and reviews at Amazon.com):

- **Dictionary of Medical Acronyms & Abbreviations** by Stanley Jablonski (Editor), Paperback, 4th edition (2001), Lippincott Williams & Wilkins Publishers, ISBN: 1560534605,  
<http://www.amazon.com/exec/obidos/ASIN/1560534605/icongroupinterna>
- **Dictionary of Medical Terms : For the Nonmedical Person (Dictionary of Medical Terms for the Nonmedical Person, Ed 4)** by Mikel A. Rothenberg, M.D, et al, Paperback - 544 pages, 4th edition (2000), Barrons Educational Series, ISBN: 0764112015,  
<http://www.amazon.com/exec/obidos/ASIN/0764112015/icongroupinterna>
- **A Dictionary of the History of Medicine** by A. Sebastian, CD-Rom edition (2001), CRC Press-Parthenon Publishers, ISBN: 185070368X,  
<http://www.amazon.com/exec/obidos/ASIN/185070368X/icongroupinterna>
- **Dorland's Illustrated Medical Dictionary (Standard Version)** by Dorland, et al, Hardcover - 2088 pages, 29th edition (2000), W B Saunders Co, ISBN: 0721662544,  
<http://www.amazon.com/exec/obidos/ASIN/0721662544/icongroupinterna>
- **Dorland's Electronic Medical Dictionary** by Dorland, et al, Software, 29th Book & CD-Rom edition (2000), Harcourt Health Sciences, ISBN: 0721694934,  
<http://www.amazon.com/exec/obidos/ASIN/0721694934/icongroupinterna>
- **Dorland's Pocket Medical Dictionary (Dorland's Pocket Medical Dictionary, 26th Ed)** Hardcover - 912 pages, 26th edition (2001), W B Saunders Co, ISBN: 0721682812,  
<http://www.amazon.com/exec/obidos/ASIN/0721682812/icongroupinterna/103-4193558-7304618>
- **Melloni's Illustrated Medical Dictionary (Melloni's Illustrated Medical Dictionary, 4th Ed)** by Melloni, Hardcover, 4th edition (2001), CRC Press-Parthenon Publishers, ISBN: 85070094X,  
<http://www.amazon.com/exec/obidos/ASIN/85070094X/icongroupinterna>
- **Stedman's Electronic Medical Dictionary Version 5.0 (CD-ROM for Windows and Macintosh, Individual)** by Stedmans, CD-ROM edition (2000), Lippincott Williams & Wilkins Publishers, ISBN: 0781726328,  
<http://www.amazon.com/exec/obidos/ASIN/0781726328/icongroupinterna>



- **Stedman's Medical Dictionary** by Thomas Lathrop Stedman, Hardcover - 2098 pages, 27th edition (2000), Lippincott, Williams & Wilkins, ISBN: 068340007X,  
**<http://www.amazon.com/exec/obidos/ASIN/068340007X/icongroupinterna>**
- **Tabers Cyclopedic Medical Dictionary (Thumb Index)** by Donald Venes (Editor), et al, Hardcover - 2439 pages, 19th edition (2001), F A Davis Co, ISBN: 0803606540,  
**<http://www.amazon.com/exec/obidos/ASIN/0803606540/icongroupinterna>**

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