THE FACTS ON FILE ENCYCLOPEDIA OF

HEALTH AND MEDICINE

IN FOUR VOLUMES:

VOLUME 2

An Amaranth Book

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To your health!

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VOLUME 2

FOREWORD

A big part of my role as a physician is educating my patients about their health. I take as much time as each person needs to explain prevention measures, test results, and treatment options. I encourage questions. But in the moment, sitting there in my office, most people do not yet know what to ask me. By the time questions flood their thoughts, they may be back at work or at home.

Numerous events and circumstances can challenge health, and we all need to know what actions we can take to keep ourselves healthy as well as to obtain appropriate treatment for health conditions that do affect us. Knowledge empowers all of us to make informed and appropriate decisions about health care. Certainly there is no shortage of reference material. Yet there is *so* much information available today! Even for physicians, it is challenging to keep up. How can you get to the core of what you want to know, reliably and to the level of detail you need?

The Facts On File Encyclopedia of Health and Medicine is a great resource for up-to-date health information presented in a manner that is both comprehensive and easy to understand no matter what your level of medical knowledge. The encyclopedia organizes entries by body system. The progression of body systems—and entries—throughout the encyclopedia presents topics the way you think about them.

Going beyond this basic structure, however, is another layer of organization that particularly appeals to me, which is a comprehensive structure of cross references that integrates entries across body systems. After all, your body functions in an integrated way; so, too, should a reference series that discusses your body's health. Not very much that happens with your health affects one part of your body in isolation from other body structures and functions. Your body attempts to compensate and adjust, often without your awareness, until it can no longer accommodate the injury or illness. The symptoms you bring to your doctor may reflect this compensation, for example frequent headaches that point not to brain tumor (as many people fear but is very rare) but to eye strain or muscle tension or sometimes to hypertension (high blood pressure).

In my medical practice I emphasize integrative health care, embracing the philosophy that health exists as the intricate intertwining of the body's many systems, structures, and functions. So, too, does the care of health. I received my medical degree from Tufts University School of Medicine in Boston, an institution noted for remaining at the forefront of the medical profession. I also completed clinical programs in Mind-Body Medicine at Harvard University, Integrative Medicine at the University of Arizona School of Medicine, and Medical Acupuncture at the University of California-Los Angeles (UCLA). I am a board-certified obstetrician-gynecologist, a board-certified clinical nutritionist, and a licensed acupuncturist. I see patients in my practice in Cincinnati, Ohio; I teach, I lecture, and I frequently go on television and radio to talk about health topics. In each of these areas, I encourage people to think about their health and health concerns from an integrative perspective. When you understand your health from multiple dimensions, you can better understand what to do to keep yourself as healthy as possible.

I wish you the best of health for all of a long, satisfying life. But when the time comes that you must make decisions about medical care, I want you to have the knowledge to make informed

choices that are right for you. Whether you start here and move on to more specialized resources or locate all the information you need within these four volumes, you will find *The Facts On File Encyclopedia of Health and Medicine* to be a most valuable reference resource.

—Maureen M. Pelletier, M.D., C.C.N., F.A.C.O.G.

HOW TO USE
THE FACTS ON FILE ENCYCLOPEDIA OF HEALTH AND MEDICINE

Welcome to *The Facts On File Encyclopedia of Health and Medicine*, a four-volume reference set. This comprehensive resource is an indispensable reference for students, allied health professionals, physicians, caregivers, lay researchers, and people seeking information about health circumstances and conditions for themselves or others. Entries present the latest health concepts and medical knowledge in a clear, concise format. Readers may easily accumulate information and build a complete medical profile on just about any health or medical topic of interest or concern.

A New Paradigm for the Health and Medical Encyclopedia

As the art and science of health and medicine continues to evolve, with complex and elegant discoveries and new techniques, medications, and treatments emerging all the time, the need has arisen for a new paradigm for the encyclopedia of health and medicine—a rethinking of the old, and increasingly outmoded, presentations. Carefully researched and compiled, *The Facts On File Encyclopedia of Health and Medicine* offers many distinguishing features that present readers and researchers with an organization as up-to-date and compelling as the breakthrough information its entries contain.

Recognizing the current emphasis on presenting a truly integrative approach to both health and disease, *The Facts On File Encyclopedia of Health and Medicine* organizes content across volumes within a distinctive format that groups related entries by body system (for example, "The Cardiovascular System") or by general health topic (for example, "Genetics and Molecular Medicine"):

- **Volume 1** presents the sensory and structural body systems that allow the body to engage with its surroundings and the external environment.
- **Volume 2** presents the cell- and fluid-based body systems that transport nutrients, remove molecular wastes, and provide protection from infection.
- **Volume 3** presents the biochemical body systems that support cellular functions.
- **Volume 4** presents topics that apply across body systems (such as "Fitness: Exercise and Health") or that address broad areas within health care (such as "Preventive Medicine").
- The appendixes provide supportive or additional reference information (such as "Appendix X: Immunization and Routine Examination Schedules").

Following Research Pathways

The Facts On File Encyclopedia of Health and Medicine's organization and structure support the reader's and researcher's ease of use. Many encyclopedia users will find all the information they desire within one volume. Others may use several or all four of the encyclopedia's volumes to arrive at a comprehensive, multifaceted, in-depth understanding of related health and medical concepts and information. Researchers efficiently look up information in *The Facts On File Encyclopedia of Health and Medicine* in several ways.

Each section's entries appear in alphabetical order (except the entries in Volume 4's "Emergency and First Aid" section, which are grouped by type of emergency). The researcher finds a desired entry by looking in the relevant volume and section. For example, the entry for **acne** is in Volume 1 in the section "The Integumentary System" and the entry for **stomach** is in Volume 3 in

the section "The Gastrointestinal System." The researcher can also consult the index at the back of the volume to locate the entry, then turn to the appropriate page in the volume.

Terms that appear in SMALL CAPS within the text of an entry are themselves entries elsewhere in *The Facts On File Encyclopedia of Health and Medicine*. Encyclopedia users can look up the entries for those terms as well, for further information of potential interest. Such SMALL CAPS cross references typically provide related content that expands upon the primary topic, sometimes leading the user in new research directions he or she might otherwise not have explored.

For example, the entry **hypertension** is in the section "The Cardiovascular System." The entry presents a comprehensive discussion of the health condition hypertension (high blood pressure), covering symptoms, diagnosis, treatment options, risk factors, and prevention efforts. Among the numerous SMALL CAPS cross references within the hypertension entry are the entries for

- **retinopathy**, an entry in the section "The Eyes" in Volume 1, which discusses damage to the eye that may result from untreated or poorly managed hypertension
- **blood pressure**, an entry in the Volume 2 section "The Cardiovascular System," which discusses the body's mechanisms for maintaining appropriate pressure within the circulatory system
- **stroke** and **heart attack**, entries in Volume 2's "The Cardiovascular System" about significant health conditions that may result from hypertension
- **kidney,** an entry in the section "The Urinary System" in Volume 3, which discusses the kidney's role in regulating the body's electrolyte balances and fluid volume to control blood pressure
- **atherosclerosis, diabetes, hyperlipidemia,** and **obesity**, entries in the sections "The Cardiovascular System" in Volume 2, "The Endocrine System" in Volume 3, and "Lifestyle Variables: Smoking and Obesity" in Volume 4, and all of which are health conditions that contribute to hypertension

Following the path of an encyclopedic entry's internal cross references, as shown above, can illuminate connections between body systems; define and apply medical terminology; reveal a broad matrix of related health conditions, issues, and concerns; and more. The SMALL CAPS cross references indicated within the text of encyclopedic entries lead encyclopedia users on wide-ranging research pathways that branch and blossom.

At the end of the entry for **hypertension** a list of cross references gathered in alphabetical order links together groups of related entries in other sections and volumes, such as **smoking cessation** in Volume 4's "Lifestyle Variables: Smoking and Obesity," to provide specific, highly relevant research strings. These *see also* cross references also appear in SMALL CAPS, identifying them at a glance. Encyclopedia users are encouraged to look here for leads on honing research with precision to a direct pathway of connected entries.

So, extensive cross-references in *The Facts On File Encyclopedia of Health and Medicine* link related topics within and across sections and volumes, in both broad and narrow research pathways. This approach encourages researchers to investigate beyond the conventional level and focus of information, providing logical direction to relevant subjects. Each cross-referenced entry correspondingly has its own set of cross references, ever widening the web of knowledge.

Using the Facts On File Encyclopedia of Health and Medicine

Each section of the encyclopedia begins with an overview that introduces the section and its key concepts, connecting information to present a comprehensive view of the relevant system of the human body or health and medical subject area. For most body systems, this overview begins with a list and drawings of the system's structures and incorporates discussion of historic, current, and future contexts.

Entries present a spectrum of information from lifestyle factors and complementary methods to the most current technologic advances and approaches, as appropriate. Text that is set apart or bold within an entry gives an important health warning, or targets salient points of interest to add layers of meaning and context. Lists and tables

collect concise presentations of related information for easy reference.

Each type of entry (mid-length and longer) incorporates consistent elements, identified by standardized subheadings:

- ***Entries for health conditions and diseases*** begin with a general discussion of the condition and its known or possible causes and then incorporate content under the subheadings "Symptoms and Diagnostic Path," "Treatment Options and Outlook," and "Risk Factors and Preventive Measures."
- ***Entries for surgery operations*** begin with a general discussion of the procedure and then incorporate content under the subheadings "Surgical Procedure," "Risks and Complications," and "Outlook and Lifestyle Modifications."
- ***Entries for medication classifications*** begin with a general discussion of the type of medication and its common uses and then incorporate content under the subheadings "How These Medications Work," "Therapeutic Applications," and "Risks and Side Effects."
- ***Entries for diagnostic procedures*** begin with a general discussion of the test or procedure and then incorporate content under the subheadings "Reasons for Doing This Test," "Preparation, Procedure, and Recovery," and "Risks and Complications."

Entries in Volume 4's section "Emergency and First Aid" are unique within the orientation of *The Facts On File Encyclopedia of Health and Medicine* in that they feature instructional rather than informational content. **These entries do *not* replace appropriate training in emergency response and first aid methods.** Rather, these entries provide brief directives that are appropriate for guiding the actions of a person with little or no first aid training who is first on the scene of an emergency.

Each volume concludes with a complete, full index for the sections and entries within the volume. Volume 4 of *The Facts On File Encyclopedia of Medicine* contains a comprehensive index for all four encyclopedia volumes that researchers can use to quickly and easily determine which volumes contain desired sections or entries.

The Facts On File Encyclopedia of Health and Medicine in Four Volumes

PREFACE TO VOLUME 2

Volume 2 of the four-volume *The Facts On File Encyclopedia of Health and Medicine* presents the body systems that nourish, cleanse, and protect the body. These are the systems of cells and fluids and the structures that transport them throughout the body. Though distinct in their functions and purposes, these systems overlap and integrate with one another in inseparable ways.

The Cardiovascular System

Volume 2 opens with "The Cardiovascular System," the structures and functions that carry blood throughout the body. An amazing pump—the heart—and miles of blood vessels—the arteries and veins—are the hallmarks of this system that mostly functions without conscious awareness save for the regular rhythm of the heartbeat.

Advances in medical technology make it possible to treat cardiovascular disease that even 30 years ago would have been fatal. Medications and devices can regulate the functions of the heart to overcome or compensate for disease and damage. Heart transplantation and mechanical heart substitutes, once the dream of surgeons but the venue of fiction, are now among the standard treatment options for some heart conditions. Many of the entries in "The Cardiovascular System" discuss these sophisticated therapeutic approaches. Yet lifestyle strongly influences cardiovascular health, which encyclopedia users will detect as a prevalent theme in this section.

The Blood and Lymph

These two fluid-based systems of the blood and the lymph have separate yet interconnected circulatory networks. The blood bridges the functions of the cardiovascular and pulmonary systems, circulating through arteries, veins, and capillaries to carry oxygen and nutrients to, and metabolic wastes from, cells throughout the body. The cells that do this work, the erythrocytes, make up about half the blood's cells and give blood its characteristic red color. The lymph network is the immune system's major highway; its cells are lymphocytes. These white blood cells lack color, giving lymph the appearance of watery milk. Lymph circulates through its own structure of lymph vessels though crosses from the lymphatic circulation to the blood circulation at two junctions, the cisterna chyli and the thoracic duct.

The Pulmonary System

The pulmonary system is the body's primary interaction with the external atmosphere. The lungs pull oxygen-bearing air deep into the body where an intricate molecular exchange takes place to load each outgoing breath with metabolic waste. The laws of physics—particularly those relating to relationships between pressure and volume, regulate the functions of the pulmonary system. The pulmonary system intimately interacts with the blood and the cardiovascular system. Without these interactions, the functions of the pulmonary system are of little value to the body. Acquired pulmonary disease often coexists with cardiovascular disease; entries in this section provide both discussion and cross-references to establish such connections.

The Immune System and Allergies

The immune system is a complex network of primarily cells and substances that circulate in the lymph and the blood and reside in the tissues. With much current research focused on HIV/AIDS and the understanding and treatment of cancer, knowledge of the immune system's functions con-

tinues to evolve at a pace not experienced since the discovery of antibiotics and vaccines. New approaches to conditions across the spectrum of health incorporate methods that use the immune system's own mechanisms to prevent and fight infection and disease.

Infectious Diseases

Infectious diseases remain a significant threat to health throughout the world. Vaccines, antibiotics, antiviral medications, and other therapies in combination with community health practices such as sanitation measures and water purity standards now can prevent or treat many infections that were fatal not so long ago. Entries in this section integrate medical treatments and lifestyle or preventive approaches, as both are essential to control the health consequences of infectious diseases.

Cancer

Cancer is a broad category of disease that can affect any body system. Current medical thinking is that cancer represents an intersection of genetic, immune, and lifestyle factors in varying mixes depending on the type of cancer. Like in the immune system, knowledge in this area is rapidly and continually changing. New treatments take advantage of new understandings. The entries in this section, "Cancer," cover topics that apply to cancer in general. Encyclopedia users will find entries for specific types of cancer in the relevant body system sections.

THE FACTS ON FILE ENCYCLOPEDIA OF

HEALTH AND MEDICINE

IN FOUR VOLUMES:

VOLUME 2

THE CARDIOVASCULAR SYSTEM

The cardiovascular system circulates BLOOD through the body to deliver nutrients and collect wastes from cells. Physician specialists who treat conditions of the HEART and blood vessels are cardiologists. This section, "The Cardiovascular System," presents an overview of the structures and functions of the cardiovascular system, a discussion of cardiovascular health and disorders, and entries about the health conditions that can affect the cardiovascular system.

Structures of the Cardiovascular System

HEART
- PERICARDIUM
- CORONARY ARTERIES
- MYOCARDIUM
- ENDOCARDIUM
- superior VENA CAVA
- inferior vena cava
- right atrium
- tricuspid valve
- right ventricle
- pulmonary valve
- right pulmonary ARTERY
- left pulmonary artery
- left atrium
- mitral valve
- left ventricle
- aortic valve
- AORTA
- SEPTUM
- SINOATRIAL (SA) NODE
- BUNDLE OF HIS
- left BUNDLE BRANCH
- right bundle branch
- Purkinje fibers
- ATRIOVENTRICULAR (AV) NODE

arteries of the head and neck
- occipital
- temporal
- CIRCLE OF WILLIS
- facial
- maxillary
- carotid

arteries of the upper torso and extremities
- brachiocephalic
- right subclavian
- left subclavian
- axillary
- brachial
- radial
- ulnar
- palmar arch

arteries of the trunk
- abdominal aorta
- intercostal
- celiac
- gastric
- hepatic
- splenic
- superior mesenteric
- inferior mesenteric
- renal

arteries of the lower torso and extremities
- common iliac
- external iliac
- internal iliac
- femoral
- deep femoral
- popliteal
- anterior tibial
- posterior tibial
- dorsal arch

veins of the head and neck
- superior sagittal sinus
- inferior sagittal sinus
- transverse sinus
- anterior facial
- external jugular
- internal jugular

veins of the upper torso and extremities
- brachiocephalic
- subclavian
- axillary
- brachial
- cephalic
- basilic

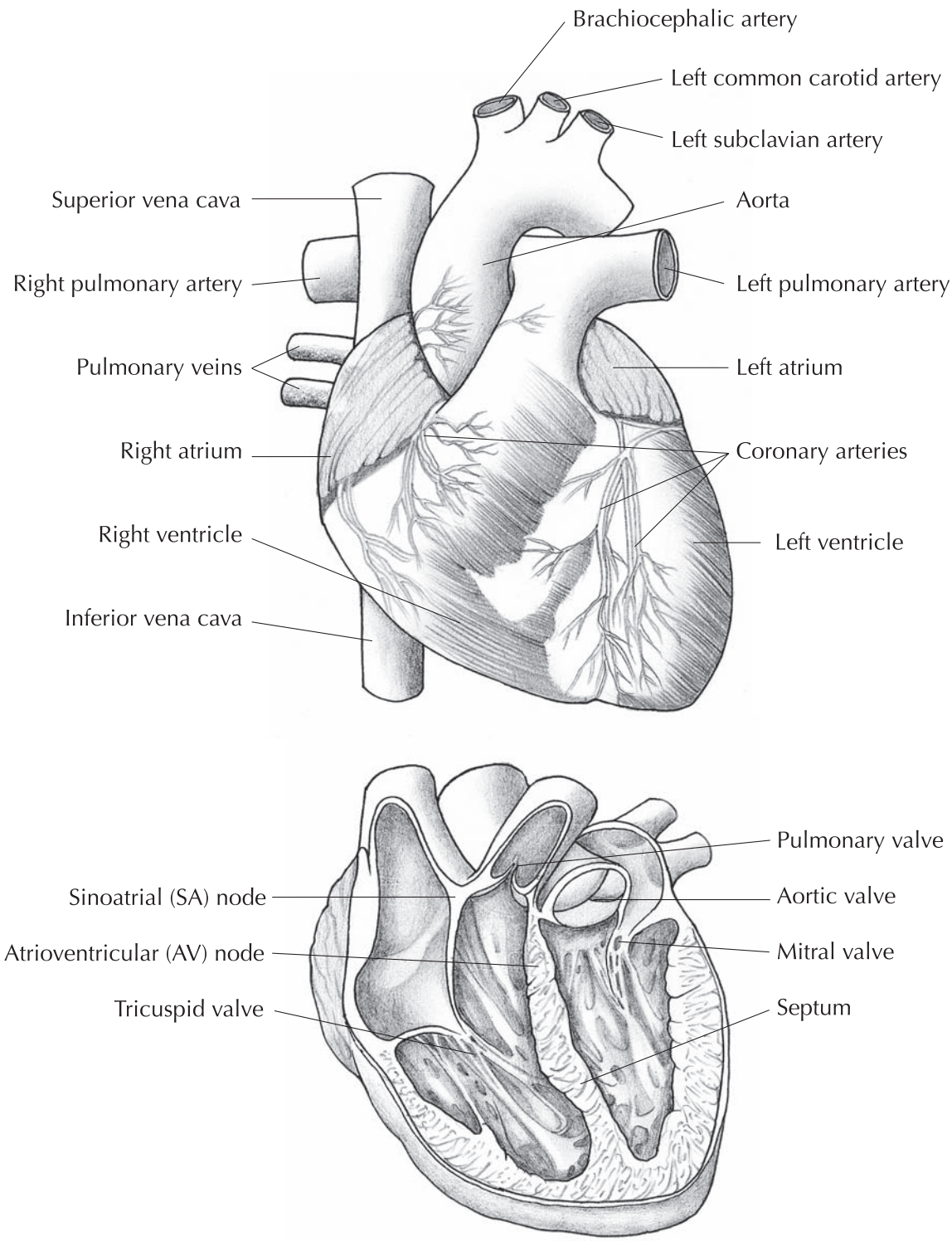
veins of the trunk
- splenic
- portal
- renal
- superior mesenteric
- inferior mesenteric
- external iliac
- internal iliac

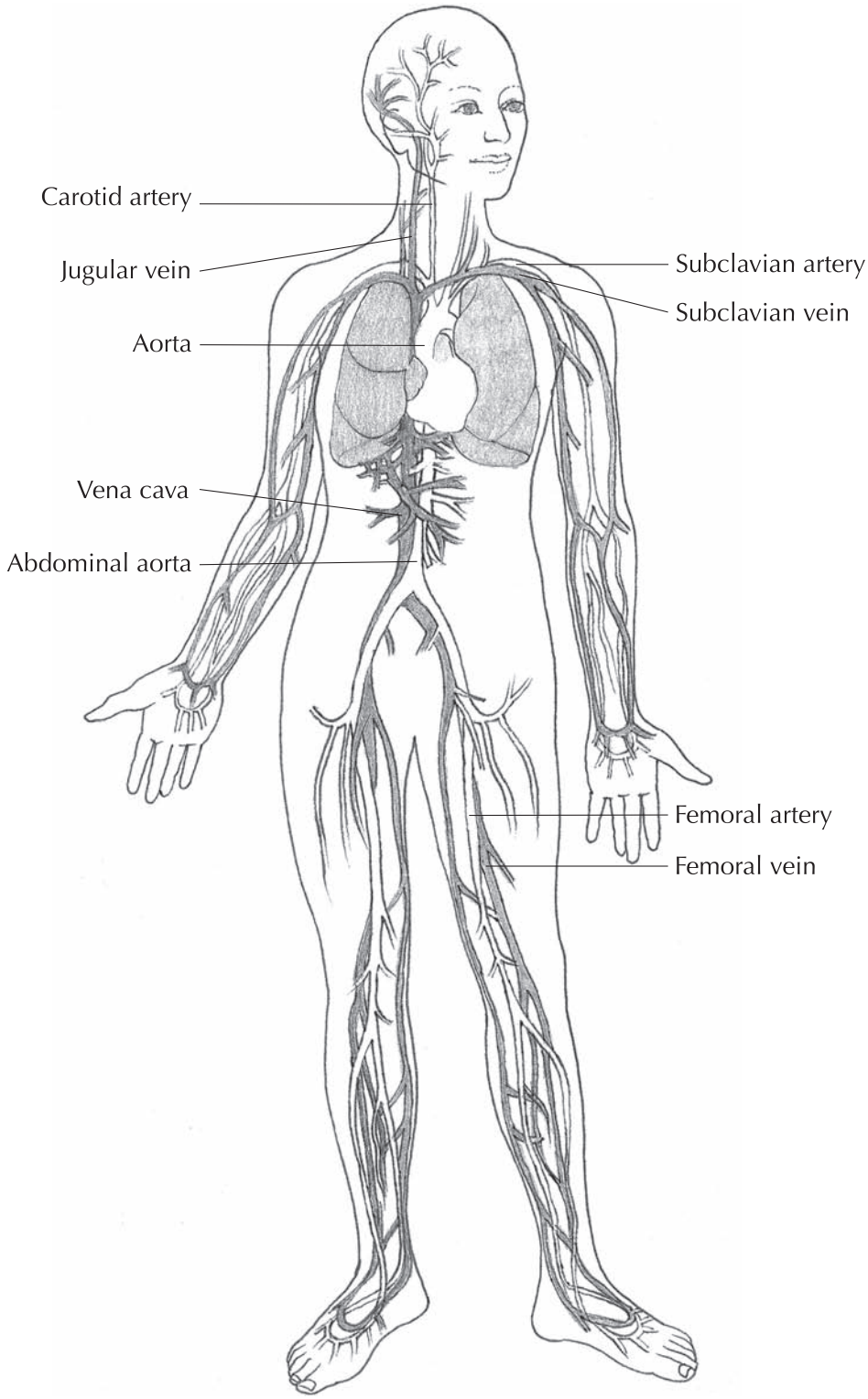
veins of the lower torso and extremities
- femoral
- popliteal
- anterior tibial
- posterior tibial
- great saphenous
- small saphenous
- dorsal arch

Functions of the Cardiovascular System

The cardiovascular system circulates blood through the body to supply cells with nutrients, notably oxygen and GLUCOSE, and to remove the waste byproducts of METABOLISM. The centerpiece of this system is the heart, a muscular organ about the size and shape of a closed fist that beats 70 to 90 times a minute in a healthy adult at rest. The body's circulation is a closed, pressurized system that contains a constant blood volume of about 10 liters (2.6 gallons). An extensive network of blood vessels–which, if stretched end to end, would traverse 100,000 miles—transports that blood through the body.

Cardiovascular function defines life and death. The cardiovascular system is among the first of


Brachiocephalic artery
Left common carotid artery
Left subclavian artery
Superior vena cava
Aorta
Right pulmonary artery
Left pulmonary artery
Pulmonary veins
Left atrium
Right atrium
Coronary arteries
Right ventricle
Left ventricle
Inferior vena cava
Pulmonary valve
Sinoatrial (SA) node
Aortic valve
Atrioventricular (AV) node
Mitral valve
Tricuspid valve
Septum


Carotid artery
Jugular vein
Aorta
Vena cava
Abdominal aorta
Subclavian artery
Subclavian vein
Femoral artery
Femoral vein

the body systems to become functional. The rudimentary heart begins beating at three weeks gestational age, and by eight weeks the heart's formation is complete. Doppler ULTRASOUND, a noninvasive procedure that uses sound waves to detect motion, can detect the fetal heartbeat at 10 to 12 weeks into PREGNANCY.

PULSE and BLOOD PRESSURE—the rate and force of blood as it flows through the arteries—are among the basic vital signs health-care providers assess to determine core health status and indeed life or death. When the heart stops beating, pulse and blood pressure cease. Cells in the BRAIN and the MYOCARDIUM, deprived of oxygen, begin to die. Though myocardial cells are capable, to an extent, of regenerating, brain cells are not. Only two to three minutes without oxygen can result in permanent neurologic damage and even death.

The heart The heart lies behind the protective enclosure of the rib cage, its left side beneath the STERNUM (breastbone) and its right side extending about to the center of the right BREAST. A tough sac, the PERICARDIUM, encases the heart. A thin layer of fluid between the pericardium and the myocardium (heart MUSCLE) allows the heart to move continuously without friction in much the same way motor oil permits pistons to glide freely within an engine. A crownlike network of arteries, the CORONARY ARTERIES, encircles the outer surface of the myocardium. This network directs roughly 20 percent of the body's blood supply and 70 percent of the blood's oxygen content to the heart with each heartbeat. A thin membrane, the ENDOCARDIUM, lines the chambers of the heart. The endocardium is so smooth not even platelets, the blood's clotting cells, can stick to it.

The heart's four chambers collect and expel blood through rhythmic, synchronized contractions. The two upper chambers, the atria, receive blood into the heart. The two lower chambers, the ventricles, pump blood from the heart. One-way valves regulate the flow and volume of blood into and out of each chamber. The four chambers of the heart contract and relax in precise coordination. The walls of the heart become progressively thicker from the atria to the ventricles, reaching their greatest density and STRENGTH in the left ventricle to support its work to contract with enough force to pump blood to the most distant cells in the body. A thick inner wall, the septum, separates the heart's chambers.

A cluster of specialized NERVE cells, the SINOATRIAL (SA) NODE, generates a "pacing" electrical impulse that starts with the right atrium and builds momentum as it courses through the cells and fibers of the myocardium. Other electrical structures—the BUNDLE OF HIS, right BUNDLE BRANCH and left bundle branch, ATRIOVENTRICULAR (AV) NODE, and the Purkinje fibers—amplify and focus the electrical impulses so they reach maximum intensity when they arrive at the left ventricle. This collective effort forms the CARDIAC CYCLE, the sequential and coordinated contraction and relaxation of the atria and the ventricles.

The right atrium and right ventricle, known collectively as the right heart, handle deoxygenated blood returning from the body. Blood flows from the superior VENA CAVA (bringing blood from the upper body) and inferior vena cava (bringing blood from the lower body) into the right atrium, which pumps it through the tricuspid valve into the right ventricle. The right ventricle pumps the blood through the pulmonary valve into the pulmonary ARTERY, which carries it to the LUNGS for OXYGENATION.

The left atrium and left ventricle, known collectively as the left heart, handle oxygenated blood. The PULMONARY VEINS (right and left, from the right lung and left lung respectively) deliver oxygenated blood from the lungs to the left atrium. The left atrium pumps the blood through the mitral valve into the left ventricle. The left ventricle propels blood through the aortic valve into the AORTA, the body's largest blood vessel, and on its circulatory journey.

The blood vessels Blood vessels circulate blood throughout the body. Arteries carry blood *from* the heart. All arteries except the pulmonary artery carry oxygenated blood; the pulmonary artery carries deoxygenated blood from the heart to the lungs. Arteries have multilayered, muscular walls that pulsate in coordination with the heart's contractions. The innermost layer, the intima, functions in the same fashion as the endocardium to keep the blood from sticking to the artery's inner walls. Veins carry blood *to* the heart. All veins except the two pulmonary veins carry deoxygenated blood; the pulmonary veins transport

oxygenated blood to the heart from the lungs. Veins have thin, flexible walls with valves that allow blood to flow only in one direction.

The smallest of the blood vessels, the arterioles and the venules, have walls fractions of a millimeter in thickness and so narrow that only the smallest of blood cells, oxygen-bearing erythrocytes, can squeeze through and even they must pass single-file. These tiny vessels mesh into the CAPILLARY BEDS, the terminus for the blood's journey. Blood cells are at their busiest here, exchanging oxygen and other nutrients for carbon dioxide and other metabolic wastes.

Most blood vessels exist in mirror structures on each side of the body and occur in parallel. The femoral artery and femoral VEIN run together, for example, one set serving each upper leg. Often these vessels have similar names, such as the femorals or the popliteal artery and popliteal vein. As the coronary arteries channel oxygenated blood to the heart, the arteries that form the CIRCLE OF WILLIS at the base of the brain direct oxygen-rich blood to the brain.

The circulation Each beat of the heart propels 80 milliliters (2.5 ounces) of blood into the AORTA, the largest artery in the body. It takes about 20 seconds for that same volume of blood to complete its journey through the body's blood vessels and return to the heart. Every minute, 5 to 6 liters (0.85 to 1.5 gallons) of blood circulates through the body—the equivalent of three 2-liter bottles of soda. In the course of a day the volume of blood the heart pumps is enough to fill an Olympic-size swimming pool.

Pressure aids the heart in pushing blood through the blood vessels. A complex interaction of hormones and other chemicals regulates blood pressure. Blood in the arteries is under high pressure, helping push it to the cells that require the oxygen and nutrients it carries. The pressure within the arteries allows blood to defy the pull of gravity as it courses to the body's tissues. Because the circulation is a closed system, the pressure of the arterial flow helps send blood through the veins as well, much as the pressure of a river's water continues to create current in the small streams that branch from it. The pressure of the blood within veins is significantly lower than the pressure within arteries. Valves in the veins act as one-way gates to keep blood flowing back to the heart. Skeletal muscles encase the major veins, further supporting them. With every movement these muscles massage the veins to help move returning blood along its passage back to the heart.

Health and Disorders of the Cardiovascular System

The cardiovascular system has the capacity to maintain healthy function in adults well into the seventh decade and beyond, though for many people it does not. More than 70 million Americans are LIVING WITH CARDIOVASCULAR DISEASE; 10 million of them are disabled to an extent that they are unable to enjoy the lifestyles they desire as a result. CARDIOVASCULAR DISEASE (CVD)—a collective term for the many health conditions that affect the heart and blood vessels—causes the deaths of more than 900,000 Americans each year, making it the leading cause of death among men and women alike in the United States. Most CVD among Americans is acquired, developing through the course of life and nearly always as a consequence of lifestyle factors. Genetic factors and other health conditions, notably DIABETES, may also contribute.

FORMS OF CARDIOVASCULAR DISEASE (CVD)

ANEURYSM	ARRHYTHMIA
ATHEROSCLEROSIS	BUNDLE BRANCH BLOCK
CARDIOMYOPATHY	CONGENITAL HEART DISEASE
CORONARY ARTERY DISEASE (CAD)	DEEP VEIN THROMBOSIS (DVT)
ENDOCARDITIS	HEART FAILURE
HYPERLIPIDEMIA	HYPERTENSION (high BLOOD PRESSURE)
HYPOTENSION (low blood pressure)	INTERMITTENT CLAUDICATION
ISCHEMIC HEART DISEASE (IHD)	KAWASAKI'S DISEASE
LONG QT SYNDROME (LQTS)	MYOCARDITIS
PERICARDITIS	PERIPHERAL VASCULAR DISEASE (PVD)
PRIMARY PULMONARY HYPERTENSION	RAYNAUD'S SYNDROME
RHEUMATIC HEART DISEASE	SICK SINUS SYNDROME
STROKE	TRANSIENT ISCHEMIC ATTACK (TIA)
VALVULAR HEART DISEASE	WOLFF-PARKINSON-WHITE SYNDROME

About 30,000 infants are born with CONGENITAL HEART DISEASE—defects of the heart and blood vessels—each year. Heart defects are the most com-

mon birth defects in the United States. Some congenital heart defects are life-threatening, such as tetralogy of Fallot and transposition of the great arteries (TGA), and require extensive surgical reconstruction or HEART TRANSPLANTATION for the infant to survive. Many congenital heart anomalies are correctable with surgery or treatable with medications, allowing the child relatively normal life experiences and life expectancy. Researchers do not know the causes of many of these defects, which arise early in embryonic development.

Though some of the most exciting technological advances in modern medicine are those that improve treatment for cardiovascular conditions such as heart failure, health experts believe lifestyle measures could prevent as much as 90 percent of acquired cardiovascular disease. Cardiovascular health depends on four key lifestyle factors:

- not smoking
- nutritious eating habits
- daily physical exercise
- maintaining healthy weight

These factors maintain the cardiovascular system in optimal health. Yet despite the overwhelming evidence that these factors do in fact prevent cardiovascular disease, two thirds of the US population is overweight and three fourths do not get the minimum recommended physical exercise. Two lifestyle-related health conditions that strongly influence cardiovascular disease are diabetes and OBESITY. Type 2 diabetes, the most common form of diabetes among American adults, and obesity are closely linked. When these two conditions coexist, some form of cardiovascular disease is almost certainly present as well.

Traditions in Medical History

The heart mystified ancient physicians. Though all cultures recognized the relationship between the heart and life itself, they differed vastly in their interpretations of what that relationship was. The Egyptians held the heart to be the base of intellect and emotion in life and the measure of that life's worth upon a person's passage to the afterworld. Mesopotamian and Sumerian physicians used MEDICINAL HERBS AND BOTANICALS to treat ailments such as pounding of the pulse and heart weakness—perhaps references to conditions contemporary doctors might diagnose as PALPITATIONS and HEART FAILURE.

Ancient Chinese physicians speculated that the heart circulated all of the body's vital substances, including air, through a complex network of vessels and passageways. Within the tenets of primitive Chinese medicine the pulse spoke to the physician, its rhythms and patterns presenting the story of the body's health and illnesses. A gifted physician could interpret hundreds of details from numerous pulse points. Intricate readings of the pulse remain integral to TRADITIONAL CHINESE MEDICINE (TCM) as practiced today.

In Western medicine, Greek and Roman physicians of antiquity postulated that the LIVER produced the body's supply of blood from the food a person ate. The veins carried the blood from the liver to the other organs, which consumed it. The arteries, in this scheme, arose from the heart though carried air. The role of the heart itself was somewhat ambiguous, with some physicians believing the heart pulled air into the arteries through pores in the skin and others that it had nothing to do with any sort of circulation but instead gave rise to emotions and thoughts.

The Greek physician GALEN (130–200) both consolidated and expanded the understandings of human anatomy and physiology of his time into the principles and practices that became the foundation of Western medicine for the ensuing 1,200 years. In Galen's view, the veins delivered to the heart blood the liver made, and the arteries carried the air drawn into the body through pores in the skin. Other pores between the chambers of the heart, according to Galen, mixed the blood and the air. Each beat of the heart then propelled this mixture through the arteries to the organs of the body. Though this schematic makes little sense in the context of current knowledge, despite its fundamental inaccuracies it came fairly on target in its projections of the body's need for oxygen and the role of the cardiovascular system to deliver it. In Galen's day, the concept was the ideal blend of the many understandings and misunderstandings about the functions of the body.

FIRST DISCOVERY OF CIRCULATION

Records survive that document the accurate perception by Arabic physician Ibn al-Nafis in 1242 of the heart's chambers and of the closed circulation of the blood. The discovery did not reach other parts of the world, however, and came to light only in the 1920s when a medical scholar uncovered an-Nafis's medical writings and drawings.

Galenism defined medical knowledge and practice into the 17th century. In 1628 English physician William Harvey (1578–1657) published the document that would become the turning point of modern Western medicine: *Exercitatio Anatomica De Motu Cordis et Sanguinis in Animalisbus*, or in English, *An Anatomical Treatise on the Motion of the Heart and Blood in Animals*. Harvey deduced, correctly, that the heart pumped the same blood repeatedly in a closed circuit through the body, with the arteries carrying oxygenated, bright blood from the heart and the veins returning deoxygenated, dark blood to the heart. *De Motu Cordis* established the basis of cardiovascular structure and function that still frames understanding of the heart's mechanical operation.

Breakthrough Research and Treatment Advances

The most significant breakthrough in cardiology was the development of the CARDIOPULMONARY BYPASS machine, successfully used for the first time in the 1950s and the cornerstone of cardiovascular surgery today. Cardiopulmonary bypass makes it possible for the cardiovascular surgeon to stop the heart, yet maintain the body's blood circulation and oxygenation. Advances in surgery techniques, technology, and pharmacology in the last decade of the 20th century made reconstructive operations for congenital heart malformations, CORONARY ARTERY BYPASS GRAFT (CABG), and even HEART TRANSPLANTATION routine offerings on the slate of treatment options. Countless people can enjoy extended, productive lives as a result.

The limited supply of donor hearts for transplantation has focused much technology research on development of a feasible artificial replacement heart that could be fully contained within the chest. In 2001 cardiovascular surgeons implanted the first of the new generation of total artificial hearts in a handful of people suffering from end-stage cardiovascular disease. Other researchers looked toward assisting, rather than replacing, ailing hearts, resulting in implanted VENTRICULAR ASSIST DEVICES (VADS) that function in coordination with the native heart. Some cardiovascular surgeons see VADs as bridge devices to sustain cardiovascular function while awaiting a donor heart for transplantation, and others as an end-stage treatment for people who have complete HEART FAILURE but are not candidates for heart transplantation because of age or other health conditions. Now an approved treatment option for end-stage heart failure, the VAD can stay in place for as long as needed.

Cardiovascular surgeons continue to explore ways to incorporate microsurgery techniques in operations such as CABG, looking to reduce the trauma of entering the chest cavity to fully expose the heart. Minimally invasive endoscopic procedures already permit operations on arteries and veins, as well as for CABG when only one coronary artery needs replacement. Cardiovascular surgeons also are beginning to apply minimally invasive techniques for valve repair and other operations on the heart.

Breakthroughs in genetics show great promise for both treatment and prevention of cardiovascular conditions in the decades ahead. Researchers have identified numerous genes responsible for heart conditions such as LONG QT SYNDROME (LQTS), certain forms of CARDIOMYOPATHY, ATHEROSCLEROSIS, and some forms of heart failure. Many of these genes interact with environmental factors such as diet and level of physical activity, contributing to rather than outright causing heart disease. Researchers are exploring ways to use GENE THERAPY to inactivate destructive genetic influences and enhance genetic influences that support or improve cardiovascular function. These influences likely explain why some people get cardiovascular diseases and others do not even when their lifestyles are similar.

Researchers also continue to unravel the mysteries of metabolism, gaining increased understanding of how exercise and nutrition affect cell function and how processes such as atherosclero-

sis get started in the body. One focus of such research is on INSULIN, which has numerous roles in the body beyond regulating glucose balance. Insulin appears to be a key factor in many functions related to cardiovascular health and disease, including cholesterol metabolism and cell activity.

Cardiology in the coming decades promises to be an intriguing blend of high-tech solutions and simple lifestyle methods. With other advances in medicine eliminating many of the circumstances that have historically resulted in early death, such as INFECTION, today's generations may be the first to fully experience the capacity of the cardiovascular system to sustain life well into the eighth decade and beyond, pushing LIFE EXPECTANCY as well as QUALITY OF LIFE to new levels.

A

aerobic fitness The efficiency with which the cardiovascular system functions to meet the oxygen needs of cells throughout the body, particularly under the increased pressure of intense physical activity or exercise. The higher a person's aerobic FITNESS LEVEL, the more air the LUNGS can take in each breath, the more oxygen that enters the BLOOD, and the more blood the HEART can eject with each contraction. The outcome is that the cardiovascular system can deliver higher concentrations of oxygen to body tissues with less effort, which increases ENDURANCE. Aerobic fitness is a key measure of cardiovascular health.

ACTIVITIES THAT IMPROVE AEROBIC FITNESS

aerobic dance	basketball	bicycling
canoeing	cross-country skiing	handball
hiking	ice skating	jogging
kayaking	racquetball	roller skating
rowing	running	shooting hoops
snowshoeing	soccer	spinning
squash	stair climbing	stationary cycling
step aerobics	swimming	tennis
treadmill	volleyball	walking

Physical activities that exercise the muscles to a level that increases the HEART RATE and BREATHING rate for a sustained time of 15 minutes or longer provide an aerobic workout for the body that strengthens cardiovascular efficiency and improves aerobic fitness. Consistency is the key to aerobic fitness. Health experts recommend aerobic activity three to four times a week, ideally in sessions that are 30 to 45 minutes long. The higher a person's aerobic fitness level, the easier it is to sustain aerobic activity for longer periods of time.

See also AEROBIC CAPACITY; AEROBIC EXERCISE; AGING, CARDIOVASCULAR CHANGES THAT OCCUR WITH; CONDITIONING; EXERCISE AND HEALTH; LIFESTYLE AND HEALTH; MUSCLE; PHYSICAL ACTIVITY RECOMMENDATIONS; PHYSICAL EXERCISE AND CARDIOVASCULAR HEALTH; WALKING FOR FITNESS.

aging, cardiovascular changes that occur with The most significant age-related changes in cardiovascular function occur at birth in both sexes and with MENOPAUSE in women. Though changes in METABOLISM occur with aging that affect all body systems, researchers now believe cardiovascular health does not inherently decline simply as a function of aging. DIABETES, OBESITY, lack of physical exercise, and cigarette smoking are the leading causes of acquired CARDIOVASCULAR DISEASE (CVD) among adults. The effects of these factors are cumulative; they are more likely to result in disease the longer they exist and the more of them are present. Accordingly, the risk for acquired cardiovascular disease increases with age because as people get older they tend to develop health conditions that set the stage for cardiovascular deterioration. Most researchers believe these risks are mutable (changeable) through lifestyle.

Cardiovascular Changes at Birth

The cardiovascular system is among the first body systems to develop in the EMBRYO, with the rudimentary HEART beginning to beat at three weeks gestational age. The heart fully forms, and a rudimentary circulatory network develops and functions, by eight weeks gestational age. Before birth, the FETUS draws its oxygen supply from its mother's BLOOD supply, in an exchange that takes place across a membrane in the PLACENTA (fetal

and maternal blood supplies do not mix). Accordingly, the fetal LUNGS do not function. Blood flows to and from the fetus through the umbilical arteries and veins (UMBILICAL CORD).

In the adult heart the right ventricle pumps blood through the PULMONARY ARTERIES to the LUNGS for OXYGENATION. The blood returns to the heart via the PULMONARY VEINS. Because the fetal lungs are nonfunctional, the fetal circulatory system bypasses the lungs. An opening (shunt) between the atria, the foramen ovale, allows blood to flow from the right atrium to the left atrium, which pumps it to the left ventricle. A small amount of blood goes from the right atrium to the right ventricle, which pumps it into the pulmonary ARTERY. A shunt between the aorta and the pulmonary artery, the ductus arteriosus, directs the blood into the aorta where it mixes with the blood the left ventricle pumps into the AORTA. With the first breath following birth the lungs inflate and the changes in pressure initiate a series of biochemical actions that cause these shunts to close, establishing blood circulation through the lungs. Within a few days of birth the ductus arteriosus becomes the ligamentum arteriosum, a strip of connective tissue that stabilizes the aorta and the pulmonary artery. The umbilical veins retreat to form the round ligament supporting the LIVER and the umbilical arteries to form ligaments that support the abdominal muscles.

Cardiovascular Changes at Menopause

Estrogen, the HORMONE responsible for female FERTILITY, is essential for lipid metabolism. The high estrogen levels that mark fertility seem to exert a protective action on a woman's cardiovascular system, lowering the likelihood for HYPERLIPIDEMIA and related health conditions such as ATHEROSCLEROSIS and CORONARY ARTERY DISEASE (CAD). During the 35 to 40 years of her fertility, a woman's risk for cardiovascular disease is a third to half that of a man of comparable age and health status. At MENOPAUSE estrogen levels drop significantly and a woman's risk for cardiovascular disease takes a significant jump. Some studies suggest that during the first five years following menopause, a woman's risk for HEART ATTACK is greater than that of a man who is of comparable age and health status.

Hormone replacement therapy (HRT) to restore estrogen levels after menopause became a standard medical approach in the 1950s. In the 1990s numerous studies revealed significant increases in the risks for BREAST CANCER and uterine CANCER associated with HRT as well as failed to find supportive evidence that HRT improved cardiovascular health in women after menopause, and health experts withdrew recommendations for its routine use. Current recommendations suggest women, like men, make nutritious eating choices, get daily physical exercise, maintain healthy weight, and not smoke as the key preventive measures to lower their risk for cardiovascular disease in midlife and beyond.

Lifestyle Choices to Maintain Cardiovascular Health

Current research strongly supports the role of lifestyle choices in maintaining cardiovascular health, even to the extent that many researchers believe appropriate choices beginning in early childhood could prevent as much as 90 percent of acquired cardiovascular disease. Healthy adults who are in their 70s and 80s who do not have any form of cardiovascular disease or other chronic health conditions do not have significant changes in cardiovascular function. Weight management, not smoking, nutritious food choices, and daily physical exercise are the cornerstones of lifestyle measures to preserve cardiovascular health. Many researchers believe the healthy cardiovascular system has the capacity to function efficiently well into the eighth decade of life and beyond.

See also CARDIOVASCULAR DISEASE PREVENTION; CONGENITAL HEART DISEASE; ESTROGENS; LIFESTYLE AND CARDIOVASCULAR HEALTH; LIGAMENT; MUSCLE; PREGNANCY; SMOKING CESSATION; WEIGHT LOSS AND WEIGHT MANAGEMENT.

aneurysm A weakened and often distended (stretched) area in the wall of an ARTERY. Though an aneurysm may develop in any artery, the most common location is the descending or abdominal AORTA. An aneurysm is potentially life-threatening. The continual pressure of the BLOOD flowing through the artery pressures the weakened area, which can cause the layers of the artery's wall to further split and separate, called a dissecting

aneurysm, or to rupture. An aneurysm that ruptures in the BRAIN causes hemorrhagic STROKE, with mild to severe consequences depending on its location and size. Fewer than 5 percent of strokes are hemorrhagic.

Aneurysms sometimes accompany congenital malformations of the blood vessels, called ARTERIOVENOUS MALFORMATIONS (AVMS), in which the arteries and veins in a particular location, usually in the brain or brainstem, form an entangled mass. Aneurysms are also common in MARFAN'S SYNDROME, a genetic disorder that affects the musculoskeletal and cardiovascular systems. Most aneurysms, however, result from atherosclerotic deposits that damage and weaken the walls of the arteries. HYPERTENSION (high BLOOD PRESSURE), when present, exacerbates the situation by exerting further pressure against the weakened area of the artery.

A ruptured aneurysm is a life-threatening emergency that requires immediate medical attention. Loss of blood can be rapid and massive.

Often an aneurysm shows no symptoms. The doctor may detect an aneurysm during a ROUTINE MEDICAL EXAMINATION or during testing or treatment for other medical conditions. Cerebral aneurysms may cause seizures, HEADACHE, or symptoms similar to stroke such as weakness on one side of the body and memory lapses or cognitive dysfunction. An abdominal or thoracic aortic aneurysm may cause PAIN (usually severe) in the area of the aneurysm. These symptoms are usually transient (come and go) though are crucial warning signs that the aneurysm is unstable. Sometimes the doctor can palpate an abdominal aneurysm, feeling its pulsations through the abdominal wall. COMPUTED TOMOGRAPHY (CT) SCAN or MAGNETIC RESONANCE IMAGING (MRI) can affirm the diagnosis. Surgery to repair the aneurysm, in which the surgeon either removes the weakened segment and sutures the healthy ends of the artery together or applies a synthetic patch over the area of weakness, is the only curative treatment. When doctors detect and repair aneurysms before they rupture, they seldom cause further health problems and require no special care after HEALING. It is important to treat the condition that may have caused the aneurysm, when possible, to prevent aneurysms from developing in other locations.

See also ATHEROSCLEROSIS; COGNITIVE FUNCTION AND DYSFUNCTION; CONGENITAL ANOMALY; CORONARY ARTERY DISEASE (CAD); GENETIC DISORDERS; LIFESTYLE AND CARDIOVASCULAR HEALTH; SEIZURE DISORDERS.

angina pectoris Chest discomfort originating from the HEART, usually resulting from restricted BLOOD flow due to CORONARY ARTERY DISEASE (CAD) that occludes (blocks) one or more of the CORONARY ARTERIES. Coronary ARTERY spasm, especially that resulting from COCAINE use, may also cause angina. Some people experience a crushing pressure that radiates into the left shoulder, arm, and THROAT. Other people experience discomfort similar to DYSPEPSIA (indigestion or heartburn). Though the nature and quality of discomfort varies among individuals, for most people angina pectoris is a chronic (long-standing) condition with predictable symptoms that appear with exertion and subside with rest.

An angina pectoris attack lasts only a few minutes, with rest bringing pronounced relief. CHEST PAIN that persists longer suggests HEART ATTACK and requires immediate medical attention.

Angina pectoris does not signal HEART ATTACK, though it is a warning that atherosclerotic accumulations in the coronary arteries have narrowed the arterial lumen (channel or opening through which blood flows) by 70 percent or more. When exercise or other stress (such as stepping out into a cold wind) increases the demand on the heart to pump more blood, the stiffened and narrowed coronary arteries, which in health could expand to nearly double the volume of blood flowing through them, cannot respond. The heart MUSCLE (MYOCARDIUM) fails to receive the oxygen it needs as well as to dispose of the metabolic wastes that are accumulating within its cells.

Treatment for angina pectoris generally combines relieving symptoms and mitigating the underlying cause. Medications to treat angina pectoris cause smooth muscle tissue (such as makes up the walls of the arteries) to relax. This allows

the coronary arteries to modestly increase the flow of blood, which usually is sufficient to ease symptoms. Commonly prescribed medications include nitrates such as nitroglycerin and isosorbide, beta antagonist (blocker) medications such as atenolol and propanolol, and calcium channel antagonist (blocker) medications such as diltiazem and verapamil. Cardiologists typically recommend ASPIRIN THERAPY for people who have angina pectoris, to help prevent MYOCARDIAL INFARCTION (blood clot that blocks the flow of blood, causing heart tissue to die).

For some people, the most effective treatment is ANGIOPLASTY to repair, or CORONARY ARTERY BYPASS GRAFT (CABG) to replace, occluded coronary arteries. However, many people who have angina pectoris remain stable with medication therapy. Cardiologists disagree about the value of CABG for people whose only symptom of disease is angina pectoris, because there is growing evidence that the risks of the surgery (including rapid occlusion of the grafts) do not counterbalance the benefits.

Two forms of angina are more serious: unstable angina and variant angina. In unstable angina, also called acute coronary insufficiency or preinfarction angina, symptoms are unpredictable and do not necessarily correlate to increased demands on the heart such as physical activity may place. Many cardiologists consider unstable angina a precursor to heart attack. With unstable angina, symptoms may occur during sleep or at rest, are often intense and extended, and progressively more severe. Sublingual (under the tongue) nitroglycerin may provide relief. As the underlying heart disease progresses, however, symptoms become more difficult to control. Angioplasty or CABG is often the most viable treatment options.

In variant angina, also called Prinzmetal's angina, spasm of a coronary artery causes symptoms that tend to occur without provocation at certain times of the day. Specific changes in the ELECTROCARDIOGRAM (ECG) accompany the symptoms. Medication (nitroglycerin or calcium channel blocker) is the most effective treatment for most people who have variant angina. CABG may relieve symptoms that do not respond to medication, though typically occlusion affects only one coronary artery to cause the symptoms. Generally the risks of OPEN HEART SURGERY, such that CABG requires, outweigh the potential benefits to replace a single coronary artery. TRANSMYOCARDIAL LASER REVASCULARIZATION (TMLR), a surgical procedure less invasive than CABG that cardiologists began using in 1998, shows promise for relieving angina that does not respond to other treatment. In TMLR, the surgeon uses a laser to pierce the left ventricle with narrow channels. As the channels heal they cause new blood vessels to develop in the myocardium, improving the flow of blood to the heart muscle.

See also INTRA-AORTIC BALLOON PUMP (IABP) COUNTERPULSATION; ISCHEMIC HEART DISEASE; MEDICATIONS TO TREAT CARDIOVASCULAR DISEASE.

angiogram A diagnostic test to visualize BLOOD vessels. The test is an angiography; the result is an angiogram. The cardiologist or vascular specialist injects dye into the relevant blood vessels to assess the flow of blood through them, observing the flow via FLUOROSCOPY (moving X-rays). Angiography is useful for diagnosing PERIPHERAL VASCULAR DISEASE (PVD), CORONARY ARTERY DISEASE (CAD), VENOUS INSUFFICIENCY, and DEEP VEIN THROMBOSIS (DVT). The cardiologist does angiography of the HEART during CARDIAC CATHETERIZATION. The risks of angiography include bleeding or INFECTION at the injection site and reaction to the dye. With the precision and availability of noninvasive imaging technology such as COMPUTED TOMOGRAPHY (CT) SCAN and MAGNETIC RESONANCE IMAGING (MRI), doctors use noncardiac angiography (angiography of peripheral blood vessels such as in the legs) primarily when the diagnosis or extent of blockage remains uncertain or before surgery to correct blockages.

See also ANGIOPLASTY; CORONARY ARTERY BYPASS GRAFT (CABG).

angioplasty A CARDIAC CATHETERIZATION procedure to widen the opening of an ARTERY, generally as treatment for ANGINA PECTORIS, CORONARY ARTERY DISEASE (CAD), or PERIPHERAL VASCULAR DISEASE (PVD). Angioplasty is most effective when the occlusion is between 70 percent and 90 percent and affects only one or two locations within the arteries. More extensive occlusion in the coronary arteries may require CORONARY ARTERY BYPASS GRAFT (CABG) to instead redirect the blood flow through replace-

ment arteries. The cardiovascular surgeon may also use angioplasty to remedy occlusions in arteries other than those supplying the HEART, such as to treat PVD affecting the larger arteries in the legs.

Procedure

Angioplasty is almost always an AMBULATORY SURGERY (same-day) procedure, or at most requires one night in the hospital for recovery and observation following the procedure. The cardiologist uses local ANESTHETIA and general SEDATION to make the person comfortable. After numbing the location with local anesthetic the cardiologist inserts a catheter into an ARTERY near the surface of the body, typically the femoral artery in the groin, and threads it into the occluded artery. Injected dye helps the cardiologist to visualize the catheter's progress using FLUOROSCOPY (moving X-ray), which displays the images on a closed circuit monitor.

Once the catheter is in position at the occlusion, the cardiologist uses a syringe to inject a small amount of sterile solution through the catheter to inflate a tiny balloon at the catheter's tip. The balloon applies pressure against the walls of the artery, expanding the channel through which blood flows. The cardiologist may deflate the balloon, advance the catheter, and reinflate the balloon to widen a larger segment of the artery. The procedure usually compresses accumulations of ATHEROSCLEROTIC PLAQUE (atheromas) to reduce their intrusion into the arterial passageway. The cardiologist may also use the catheter to place a STENT, a tiny springlike device that maintains pressure against the arterial wall to help maintain the widened channel in the artery at the site of the compressed atheroma.

Risks and Complications

Risks during the angioplasty include HEART ATTACK or STROKE from dislodged atherosclerotic plaque (which is rare), excessive bleeding, trauma to the artery, and irritation of the heart that causes ARRHYTHMIA. The cardiac catheterization facility or hospital where the cardiologist performs the angioplasty is equipped and staffed for immediate cardiac surgery if necessary. More common complications are bleeding and PAIN at the catheter insertion site, or INFECTION following the procedure. The cardiologist may choose to administer prophylactic ANTIBIOTIC MEDICATIONS, particularly in people who are at risk for bacterial ENDOCARDITIS.

The most common complication of angioplasty is restenosis (reclosure) of the artery, either from the compressed atheroma reexpanding or from continued atherosclerotic processes that create new atheromas. About half of people who undergo angioplasty experience restenosis within two years. About a quarter have clinically significant restenosis within six months and must have a repeat angioplasty or CABG to restore blood flow to the heart. Repeat angioplasty is generally less successful, and carries a higher risk of damage to the artery. As atherosclerosis progresses, which it tends to do, other coronary arteries occlude as well.

Outlook and Lifestyle Modifications

Angioplasty is a temporary measure for most people, providing relief of symptoms for six months to two or three years. However, angioplasty does not treat the underlying disease process, which is likely to continue even with medical interventions such as lipid-lowering medications to slow its progress. Most arteries tend to reocclude. Some people are able to undergo multiple angioplasty procedures over time though others must look to different treatment options such as CABG. The most effective outcomes are those that follow the angioplasty with lifestyle changes to improve cardiovascular health such as WEIGHT LOSS AND WEIGHT MANAGEMENT, daily physical activity, and SMOKING CESSATION.

See also ATHERECTOMY; DIABETES AND CARDIOVASCULAR DISEASE; MEDICATIONS TO TREAT CARDIOVASCULAR DISEASE; PHYSICAL EXERCISE AND CARDIOVASCULAR HEALTH; SURGERY BENEFIT AND RISK ASSESSMENT.

anticoagulation therapy Prophylactic (preventive) treatment with medications to reduce the risk of BLOOD clots, broadly including approaches that inhibit various stages of COAGULATION. Anticoagulation therapy is common treatment for a number of cardiovascular conditions including ATRIAL FIBRILLATION, INTERMITTENT CLAUDICATION, DEEP VEIN THROMBOSIS (DVT), PULMONARY EMBOLISM, and VALVULAR HEART DISEASE, and following MYOCARDIAL INFARCTION (HEART ATTACK) and cerebral infarction (ischemic or thromboembolic STROKE). Anticoagulant medications prevent new clots from forming

and existing clots from getting larger, though cannot dissolve clots that already exist. Medications that dissolve existing clots are called thrombolytic agents, which have different pharmacologic actions in the body.

The appropriate anticoagulation therapy depends on the reason for the therapy (health condition), the person's overall health situation, and any other medications the person needs to take. Doctors may prescribe anticoagulation therapy for noncardiovascular reasons such as after orthopedic surgery, particularly JOINT REPLACEMENT. People commonly refer to anticoagulant medications as "blood thinners," though this is a misnomer because these medications do not alter the blood's viscosity (thickness).

Antiplatelet Agents

Antiplatelet medications, also called PLATELET inhibitors, slow clot formation by inhibiting PLATELET AGGREGATION. These medications are especially effective in people who have increased risk for CORONARY ARTERY DISEASE (CAD) or thromboembolic stroke. Platelets are the cells in the blood that are first on the scene of any injury in the body. They swarm in response to even the slightest of damage, such as the irritation and INFLAMMATION atheromas cause to the walls of the arteries. When they aggregate, or clump together, they release chemical signals that activate the sequence of events resulting in clot formation. Antiplatelet medications interfere with these chemical signals.

The most commonly used antiplatelet therapy is ASPIRIN THERAPY. Aspirin inhibits PROSTAGLANDINS, chemicals that platelets require to enable them to aggregate or stick together. Aspirin delays clotting by delaying platelet aggregation, which is the first step in the coagulation process. Platelets may come together but not stick, drifting away from each other again before they initiate the clotting process. Other commonly prescribed antiplatelet medications include clopidogrel (Plavix), ticlopidine (Ticlid), dipyridamole (Persantine), and cilostazol (Pletal). These medications may have serious side effects or interact with other medications. Ticlopidine may cause a rare but life-threatening condition, thrombotic thrombocytopenic purpura (TTP), and requires frequent blood tests to monitor for its development.

Clotting Factor Inhibitors

Other medications act to interfere with the body's ability to activate blood proteins essential for clotting (CLOTTING FACTORS). The most commonly used oral medication, warfarin (Coumadin), works by blocking one of the steps in the body's process to produce VITAMIN K. Vitamin K is essential to the metabolic processes that activate clotting factors II, VII, IX, and X. The gastrointestinal tract does not absorb heparin, which is available only in injectable form (intravenous or subcutaneous). Heparin prevents the conversion of prothrombin (clotting factor II) to thrombin, a crucial and early step of coagulation. Both of these medications are NARROW THERAPEUTIC INDEX (NTI) drugs that require very close monitoring to maintain their doses within therapeutic range. Internal bleeding, especially from the gastrointestinal tract, can occur when doses are too high. Excessive bleeding from wounds, such as ACCIDENTAL INJURIES, or from routine dental procedures, such as prophylactic cleaning, is also a risk.

Low molecular weight heparin (LMWH), also only in injectable form, acts similarly to heparin though without many of heparin's undesired side effects. Several kinds of LMWH, also called fractionated heparin, are available. Each has unique characteristics and though all are LMWH drugs, they are not interchangeable. LMWH products include dalteparin (Fragmin), enoxaparin (Lovenox), and tinzaparin (Innohep). Another injectable medication, fondaparinux (Arixtra), inhibits clotting factor X. Proper site selection and injection technique are important for people who use injectable forms of anticoagulant medications.

Benefits, Risks, and Lifestyle Modifications

Anticoagulant medications, whether antiplatelet or inhibitor, are preventive for blood clots and the health problems blood clots can cause, such as stroke, HEART attack, pulmonary embolism, and DVT. The primary risk of anticoagulation therapy is excessive or prolonged bleeding, which can be serious or life-threatening in some situations. Doctors carefully monitor blood clotting times and other measures to maintain an appropriate therapeutic balance. Spontaneous nosebleed (EPISTAXIS), easy bruising, bleeding from the gums when brushing the teeth, and blood in the stool are signs

ANTICOAGULANT MEDICATIONS

Medication	Action	Common Reasons Prescribed
aspirin	antiplatelet	HEART ATTACK and STROKE PROPHYLAXIS ATRIAL FIBRILLATION
cilostazol	antiplatelet	INTERMITTENT CLAUDICATION PERIPHERAL VASCULAR DISEASE (PVD)
clopidogrel	antiplatelet	heart attack and stroke prophylaxis atrial fibrillation
dalteparin	clotting factor inhibitor; low molecular weight heparin (LMWH)	DEEP VEIN THROMBOSIS (DVT) and PULMONARY EMBOLISM (PE) prophylaxis after major surgery that limits mobility during recovery
dipyridamole	antiplatelet	in combination with aspirin for heart attack and stroke prophylaxis in combination with warfarin after heart valve replacement to prevent clots from forming on the prosthetic valve
enoxaparin	clotting factor inhibitor; LMWH	DVT and PE prophylaxis after major surgery that limits mobility during recovery
fondaparinux	clotting factor inhibitor; blocks clotting factor X	DVT and PE prophylaxis after major surgery that limits mobility during recovery
heparin	clotting factor inhibitor	during OPEN HEART SURGERY after major surgery that limits mobility during recovery DVT and PE prophylaxis
ticlopidine	antiplatelet	stroke prophylaxis in people who cannot take aspirin or who have had previous strokes
tinzaparin	clotting factor inhibitor; LMWH	DVT and PE prophylaxis after major surgery that limits mobility during recovery
warfarin	clotting factor inhibitor; blocks VITAMIN K SYNTHESIS	intermittent claudication PVD atrial fibrillation

of excessive anticoagulation that require a doctor's evaluation.

When on anticoagulation therapy it is important to avoid OVER-THE-COUNTER (OTC) DRUGS such as NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) in products for PAIN relief, menstrual cramps, and cold and flu relief, and salicylates such as Pepto-Bismol. These products have mild anticoagulation effects that can cause excessive bleeding in combination with anticoagulation medications. As well, anticoagulation medications interact with numerous other medications and may have side effects, some of which can have serious health consequences.

Many people who are on anticoagulation therapy have underlying cardiovascular conditions that would benefit from lifestyle modifications as well, such as increased physical activity and SMOKING CESSATION. Regularly stretching the muscles throughout the day, especially leg muscles, and walking for 5 to 10 minutes every few hours help keep blood from pooling and clotting.

See also ARRHYTHMIA; GASTROINTESTINAL BLEEDING; LIFESTYLE AND CARDIOVASCULAR HEALTH; THROMBOCYTOPENIA; THROMBOLYTIC THERAPY.

aorta The ARTERY that carries BLOOD from the HEART to the body. The largest blood vessel in the body, the aorta arises from the left ventricle. At its widest point the aorta is about one and a half inches in diameter. As the aorta leaves the heart it ascends to curve behind the right atrium. The first arteries to branch from the base of the ascending aorta are the right and left CORONARY ARTERIES that supply the heart MUSCLE (MYOCARDIUM) with blood. Branching from the arch as the aorta crests over the heart are the three arteries that carry blood to the upper body:

- the brachiocephalic artery (also called the innominate artery), which transports blood to the right arm and right side of the BRAIN, head, and face
- the left common carotid artery, which transports blood to the left side of the brain, head, and face
- the left subclavian artery, which transports blood to the left arm

The aorta then crosses over the PULMONARY ARTERIES and drops behind the heart to descend through the chest and into the abdomen, aligned along the front of the spine, branching into the iliac arteries at the top of the pelvis. Numerous arteries branch from the descending aorta along its passage from the chest to the abdomen, supplying vital organs such as the LIVER, kidneys, STOMACH, and intestines. Acquired cardiovascular conditions that can affect the aorta include ATHEROSCLEROSIS, ANEURYSM, and AORTIC STENOSIS. A number of congenital malformations also can affect the aorta, including aortic coarctation, tetralogy of Fallot, and transposition of the great arteries (TPA). Most aortic conditions require surgical repair.

For further discussion of the aorta within the context of cardiovascular structure and function, please see the overview section "The Cardiovascular System."

See also CONGENITAL HEART DISEASE; PULMONARY VEINS; VENA CAVA.

aortic stenosis Narrowing of the aortic valve that restricts the flow of BLOOD from the heart's left ventricle to the AORTA. Aortic stenosis may be congenital or acquired; in either, it tends to show symptoms later in life. Acquired aortic stenosis develops as a consequence of calcium and arterial plaque deposits that infiltrate the aortic valve. Untreated aortic stenosis results in left ventricular hypertrophy (enlargement of the left ventricle), diminished CARDIAC OUTPUT, and ultimately congestive HEART FAILURE.

Symptoms of aortic stenosis may include PALPITATIONS, ANGINA PECTORIS, fatigue, SYNCOPE (fainting), and unexplained inability to participate in aerobic activities. The diagnostic path typically includes ECHOCARDIOGRAM and CARDIAC CATHETERIZATION. Treatment is surgery to replace the damaged aortic valve. After valve replacement most people experience dramatic relief from symptoms and are able to return to regular activities. Sometimes medications are necessary to treat companion conditions such as HEART failure. As with other valve operations, aortic valvuloplasty or prosthesis increases the risk for blood clots to form. Most people will need to take ANTICOAGULATION THERAPY to mitigate this risk.

See also ANTIBIOTIC PROPHYLAXIS; CONGENITAL HEART DISEASE; RHEUMATIC HEART DISEASE; VALVULAR HEART DISEASE.

apolipoprotein B100 (apoB100) A protein on the surface of lipid molecules that directs the lipid's route of METABOLISM. ApoB100 occurs primarily on low-density lipoprotein (LDL) molecules, the form of cholesterol with the highest risk for CORONARY ARTERY DISEASE (CAD). The normal level of apoB100 in the blood is 40 to 125 milligrams per deciliter (mg/dL). Elevated levels suggest familial HYPERLIPIDEMIA. ApoB100 levels also rise after MYOCARDIAL INFARCTION, when there is

damage to the HEART MUSCLE. Elevated apoB100 levels convey an increased risk for ATHEROSCLEROSIS and CAD.

See also CARDIOVASCULAR DISEASE PREVENTION; CHOLESTEROL BLOOD LEVELS; HYPERLIPIDEMIA; RISK FACTORS FOR CARDIOVASCULAR DISEASE.

arrhythmia Irregularity or abnormality of the heart's contractions. Arrhythmias can result from numerous causes including electrical disturbances of the heart's pacing mechanisms, physical damage to the HEART such as might occur with HEART ATTACK, interruptions of the heart's BLOOD supply that cause myocardial HYPOXIA (oxygen depletion), severe electrolyte imbalances, and medication side effects. COCAINE use can initiate sudden and fatal arrhythmias. Because all myocardial cells have the ability to initiate electrical impulses, it is sometimes difficult for cardiologists to determine what causes an arrhythmia.

The most common kinds of arrhythmias are

- bradycardia, in which contractions are slower than normal (typically fewer than 60 beats per minute at rest in a person whose level of routine physical activity is low)
- tachycardia, in which contractions are faster than normal (typically greater than 100 beats per minute at rest in a person whose level of routine physical activity is low)
- fibrillation, in which contractions are rapid, erratic, and nonproductive
- premature or extra beats, in which contractions occur in addition to the heart's regular contractions

The seriousness of an arrhythmia depends largely on whether it is atrial or ventricular. Typically ventricular arrhythmias are more significant and potentially hazardous than atrial arrhythmias. The most common arrhythmia that requires treatment is ATRIAL FIBRILLATION, which health experts estimate affects about one in five American adults over age 60 and which accounts for about 15 percent of strokes. The most deadly arrhythmia is VENTRICULAR FIBRILLATION, which results in seriously slowing or even halting the flow of blood to the body because the ventricles cannot pump in a coordinated manner. Some arrhythmias are transient (come and go), and others cause no symptoms or effect on cardiovascular function.

VENTRICULAR FIBRILLATION is a medical emergency that can result in death within minutes without appropriate treatment (DEFIBRILLATION).

Symptoms and Diagnostic Path

Arrhythmias may cause a range of symptoms or no symptoms at all. The most common symptoms are

- PALPITATIONS, which feel like the heart is thumping or "skipping" a beat
- weakness, lightheadedness, or fainting
- shortness of breath with exertion (DYSPNEA)
- CHEST PAIN

It is not possible to know only from the symptoms what kind of arrhythmia is present. Only an ELECTROCARDIOGRAM (ECG), a test that records the heart's electrical activity, can present the information a cardiologist needs to determine the diagnosis. The cardiologist may desire further diagnostic procedures to identify any underlying causes, as the findings may influence treatment options and decisions. Arrhythmias resulting from CORONARY ARTERY DISEASE (CAD) or HEART FAILURE, for example, require different treatment than those resulting from idiopathic electrical disturbances (problems with the heart's pacing mechanisms that have no apparent cause). Occasionally the doctor detects an arrhythmia during examination for other health concerns, which requires subsequent evaluation to determine whether, as it is not causing symptoms, it is a condition that warrants treatment.

Treatment Options and Outlook

CAFFEINE and ALCOHOL consumption can cause palpitations and other minor, benign arrhythmias, as can intense stress. Making lifestyle changes to reduce or eliminate these factors typically ends the arrhythmias related to them. Arrhythmias that are not clinically significant (those that cause no symptoms or disruptions of cardiovascular function) do not require treatment, though cardiologists generally want to monitor them to make sure

they remain benign. Antiarrhythmia medications successfully treat the majority of symptomatic arrhythmias. These medications work by blocking certain aspects of the biochemical functions responsible for myocardial contractions. The cardiologist may prescribe two or more antiarrhythmia medications in combination to treat some kinds of arrhythmias. People who have heart failure, CAD, valvular disease, and other heart disorders may take antiarrhythmia medications along with other medications to treat these conditions.

Cardiologists select antiarrhythmia medications based on the characteristics of the arrhythmia, which may be simple or complex, as well as the presence of other cardiovascular conditions, any other medications the person may be taking, and factors such as age and lifestyle. After starting antiarrhythmia therapy, it is important to continue until the cardiologist makes changes in the therapeutic approach. Suddenly stopping an antiarrhythmia medication can have significant consequences including serious arrhythmias.

Antiarrhythmia medications can have serious side effects such as worsening the existing arrhythmia or causing new arrhythmias. Some medications work by causing heart block, for example, to interrupt the conduction of aberrant electrical impulses. Finding the right medication or combination of medications sometimes takes a period of trial regimens and dosages. As the condition responsible for the arrhythmia changes over time, sometimes it becomes necessary to change the medication regimen as well.

Other interventions may become necessary if medications are ineffective or generate intolerable side effects. Such interventions may include

- CARDIOVERSION, in which the cardiologist delivers (under sedation) a mild electrical shock through the chest wall to reorganize and restore to normal the heart's electrical activity
- RADIOFREQUENCY ABLATION, a cardiac catheterization procedure in which the cardiologist uses radiofrequency impulses to kill a small and carefully targeted segment of myocardial cells to prevent them from initiating or conveying electrical impulses
- implantable PACEMAKER, a small battery-operated device that emits an electrical impulse to trigger the heart's contractions

COMMONLY PRESCRIBED ANTIARRHYTHMIA MEDICATIONS

Beta Blockers		
acebutolol (Sectral)	atenolol (Tenormin)	betaxolol (Kerlone)
carteolol (Cartrol)	esmolol (Brevibloc)	labetalol (Normodyne)
metoprolol (Lopressor)	nadolol (Corgard)	penbutolol (Levatol)
pindolol (Visken)	propranolol (Inderal)	sotalol (Betapace)
timolol (Blocadren)		
Calcium Channel Blockers		
amlodipine (Norvasc)	bepridil (Vascor)	diltiazem (Cardizem)
felodipine (Plendil)	isradipine (DynaCirc)	nicardipine (Cardene)
nifedipine (Procardia)	nimodipine (Nimotop)	nisoldipine (Sular)
verapamil (Isoptin)		
Miscellaneous Actions		
adenosine	digoxin	
Potassium Channel Blockers		
amiodarone (Cordarone)	dofetilide (Tikosyn)	ibutilide (Corvert)
Sodium Channel Blockers		
disopyramide (Norpace)	flecainide (Tambocor)	lidocaine (Xylocaine)
mexiletine (Mexitil)	moricizine (Ethmozine)	procainamide (Procan)
propafenone (Rythmol)	quinidine (Cardioquin)	tocainide (Tonocard)

- IMPLANTABLE CARDIOVERTER DEFIBRILLATOR (ICD), which functions both to deliver pacing impulses and shocking impulses to convert an arrhythmia that extends beyond certain parameters

Most people are able to successfully control or eliminate arrhythmias with appropriate treatment, resulting in no changes to lifestyle or quality of life.

Risk Factors and Preventive Measures

Most arrhythmias arise as a consequence of other CARDIOVASCULAR DISEASE (CVD) or are idiopathic (without identifiable cause). Some arrhythmia disorders are congenital or genetic, such as LONG QT SYNDROME (LQTS). People who have one kind of arrhythmia are prone to developing others. Prompt medical evaluation of symptoms that could signal cardiovascular disease or arrhythmias is important, as early detection and treatment may head off consequences such as CARDIAC ARREST or SUDDEN CARDIAC DEATH.

See also AUTOMATED EXTERNAL DEFIBRILLATOR (AED); BUNDLE BRANCH BLOCK; CARDIOPULMONARY RESUSCITATION (CPR); GENERIC DRUG; PAROXYSMAL ATRIAL TACHYCARDIA (PAT); PREMATURE VENTRICULAR CONTRACTION; STRESS AND STRESS MANAGEMENT; STROKE; TORSADE DE POINTES; WOLFF-PARKINSON-WHITE SYNDROME.

arteriosclerosis A degenerative condition of the arteries in which the walls of the arteries become stiff and rigid. Arteriosclerosis is a leading factor in age-related HYPERTENSION (high BLOOD PRESSURE). There are three forms of arteriosclerosis:

- ATHEROSCLEROSIS in which arterial plaque deposits infiltrate the inner layer of the arterial wall
- Mönckeberg's arteriosclerosis or medial calcific sclerosis, in which the medial layer of the arterial wall accumulates calcium deposits that cause the ARTERY to become rigid
- arteriolosclerosis in which the arterioles (the threadlike arteries that form the arterial portion of the CAPILLARY BEDS) lose their FLEXIBILITY and elasticity

The primary causes of arteriosclerosis include cigarette smoking (NICOTINE is highly toxic to the smooth MUSCLE fibers of the arteries), DIABETES, and hypertension. The consequences of arteriosclerosis, particularly atherosclerotic, include increased risk for HEART ATTACK, STROKE, ANEURYSM, and increased hypertension. People often use the terms atherosclerosis and arteriosclerosis interchangeably, which is not quite accurate though is correct about 90 percent of the time because atherosclerosis is the most common form of arteriosclerosis.

See also DIABETES AND CARDIOVASCULAR DISEASE; HYPERLIPIDEMIA; LIFESTYLE AND CARDIOVASCULAR HEALTH.

arteriovenous malformation (AVM) A congenital deformity in which an entanglement of arteries and veins forms. Rather than connecting into CAPILLARY BEDS that form between them, the arteries and veins in an AVM connect directly to one another. Veins lack the structure to accommodate the pressure BLOOD is under as it flows through the arteries and over time may become weakened and rupture. The resulting bleeding can be life-threatening, depending on the size and location of the AVM. Most AVMs are in the BRAIN, although an AVM can occur in other parts of the body. Though AVMs are present at birth, many do not show symptoms until later in life, even adulthood.

The symptoms of AVM vary and often are vague, making diagnosis sometimes difficult. Cerebral AVMs (AVMs in the brain) may cause HEADACHE, seizures, and STROKE-like symptoms if they apply pressure to surrounding brain tissue or if they bleed. HEMORRHAGE in the brain can cause permanent damage to the brain, resulting in PARALYSIS, cognitive loss, or death. AVMs elsewhere in the body may cause PAIN or bleeding; hemorrhagic bleeding is life-threatening. COMPUTED TOMOGRAPHY (CT) SCAN and magnetic resonance angiography, which combines MAGNETIC RESONANCE IMAGING (MRI) with dye injected into the blood vessels, are the key diagnostic procedures to detect AVM.

Treatment depends on the size and location of the AVM and may include surgery to remove the web of blood vessels, injection of a substance to block the flow of blood through the AVM (embolization), or RADIOFREQUENCY ABLATION to close off the blood vessels. Treatment often carries signif-

icant risk of uncontrolled bleeding because of the unstable nature of the AVM, and sometimes the risk of attempting treatment is greater than the risk of leaving the AVM untreated. Treatment that successfully removes or seals the AVM ends the threat of hemorrhage.

See also ANEURYSM; ARTERY; BIRTH DEFECTS; CONGENITAL ANOMALY; VEIN.

artery A flexible, muscular BLOOD vessel that carries blood from the HEART and oxygenated blood to tissues throughout the body. The wall of an artery has three layers:

- adventitia, the outermost layer, which is primarily connective tissue that gives the artery its FLEXIBILITY
- media, the middle layer, which is mostly smooth MUSCLE tissue that gives the artery the ability to contract and relax
- intima, the inner layer, which is epithelial tissue that provides a smooth surface to facilitate the flow of blood

The adventitia is more prominent in larger arteries such as the AORTA and the carotid arteries, encasing the artery in a weblike fashion without clear direction to its fibers. In smaller arteries, the media often dominates the artery's structure. The muscle fibers of the media encircle the artery, helping strengthen and stabilize the artery's walls. The delicate intima contains two structural levels, the basement or foundation membrane and the subepithelial layer, both of which run lengthwise. Each may be only a cell's thickness in small arteries, indistinguishable without magnification.

The intima's two-level structure gives the artery its ability to carry blood cells without having them stick to its inner walls. However, it also makes the artery vulnerable to ATHEROSCLEROSIS, which develops between the intima's two levels. The tiniest of the body's arteries, about the thickness of a hair, are arterioles. The body's largest artery is the aorta, which carries blood from the heart to the network of arteries that then carry the blood throughout the body.

Fibrous sheaths enclose most of the body's arteries, usually along with the companion VEIN and NERVE. These sheaths often parallel skeletal structures for protection and stability, or run deep within the body. Arteries also receive blood themselves from other arteries, which deliver oxygen and other nutrients to the layers of the artery, and contain nerves that deliver the signals to constrict or dilate. The walls of the arteries constrict and dilate in wavelike contractions that coordinate with the heartbeat to help push blood through the body. These pulsations are detectable as the PULSE at points where the artery is near the surface of the skin, such as at the wrist and the groin.

For further discussion of the artery within the context of cardiovascular structure and function, please see the overview section "The Cardiovascular System."

See also ARTERIOVENOUS MALFORMATION (AVM); ATHEROSCLEROSIS; ARTERIOSLCEROSIS; CAROTID BRUIT; CAROTID STENOSIS; CORONARY ARTERY DISEASE (CAD).

aspirin therapy A form of ANTICOAGULATION THERAPY to help prevent BLOOD clots from developing, which doctors prescribe as a prophylactic measure for HEART ATTACK and STROKE. Aspirin has a moderate anticoagulation effect. It interferes with PLATELET AGGREGATION, the first step in the clotting process. Aspirin blocks the body's production of PROSTAGLANDINS, chemicals the platelets need to help them aggregate (clump together). Cardiologists generally recommend aspirin therapy for:

- men between the ages of 40 and 75
- women who are beyond MENOPAUSE
- men and women under age 40 who have HYPERTENSION, DIABETES, or OBESITY
- men and women under age 40 who smoke cigarettes

People who do not have increased risk for CARDIOVASCULAR DISEASE (CVD)—are under age 40 and have no predisposing health conditions or lifestyle factors—likely do not receive enough benefit from aspirin therapy to offset the potential risks. The primary risks of aspirin therapy are gastrointestinal upset and excessive bleeding. Aspirin may cause GASTROINTESTINAL BLEEDING in people who have PEPTIC ULCER DISEASE, and extended bleeding during dental procedures and surgeries or with wounds such as lacerations. Doctors recommend a DOSE of

81 milligrams (mg) daily (one "baby" aspirin tablet) or 325mg milligrams every other day (one "regular" aspirin). Some products are available at 162mg strength, marketed specifically for aspirin therapy.

Call 911 at the first sign of HEART ATTACK. Do not wait for an aspirin to relieve the PAIN of a heart attack. An aspirin will only help to limit blood clotting during the heart attack. It will not help the pain.

Aspirin may also limit the damage of a HEART attack that is under way. Cardiologists recommend that people who experience symptoms of heart attack first call 911 for emergency medical aid and then chew an aspirin tablet. Chewing the aspirin tablet gets it into the bloodstream more quickly than swallowing. Studies show this approach releases enough of a burst of anticoagulant into the blood to help prevent fibrin and other clotting substances from adhering to the blockage in the coronary artery that is causing the symptoms. This small action can significantly reduce the amount of heart tissue that suffers oxygen deprivation and possible death during a heart attack.

See also CARDIOVASCULAR DISEASE PREVENTION; CORONARY ARTERIES; DEEP VEIN THROMBOSIS (DVT); RISK FACTORS FOR CARDIOVASCULAR DISEASE.

atherectomy A surgical procedure, done via CARDIAC CATHETERIZATION, to remove patches of arterial plaque (ATHEROSCLEROTIC PLAQUE), called atheromas, from the inner walls of major arteries such as the CORONARY ARTERIES. The cardiologist uses either a laser to vaporize or a rotary burr on the end of the catheter to shave away the atheromas. Often the cardiologist follows the atherectomy with balloon ANGIOPLASTY and STENT placement to help keep the ARTERY open, as atheromas tend to redevelop. Risks of atherectomy include STROKE and HEART ATTACK from debris particles that break away and become lodged in the arteries of the BRAIN or the HEART.

See also ENDARTERECTOMY; SURGERY BENEFIT AND RISK ASSESSMENT.

atherosclerosis Accumulation of lipids and other materials (ATHEROSCLEROTIC PLAQUE) between the two layers of an artery's inner wall, the intima. Over time the accumulations form brittle, hard deposits called atheromas that thicken the intima and the media (the middle of the arterial wall's three layers). The usual consequence is that the ARTERY becomes stiff and less flexible, and its inner channel, the lumen, narrows. The combined effect limits the ability of the artery to dilate or constrict, increasing the pressure necessary to push BLOOD through the artery. The result is CARDIOVASCULAR DISEASE (CVD), including HYPERTENSION (high BLOOD PRESSURE), CORONARY ARTERY DISEASE (CAD), and PERIPHERAL VASCULAR DISEASE (PVD). Atherosclerosis takes decades to develop. Many researchers believe the process of atherosclerotic accumulation begins in late childhood.

Atherosclerosis will most commonly affect medium-size arteries such as the CORONARY ARTERIES that supply the HEART, the carotid arteries that supply the BRAIN, and the primary arteries that supply the legs. Atherosclerosis can also develop in the large arteries, notably the AORTA. Atherosclerosis in the aorta presents a significant risk for aortic ANEURYSM, a potentially life-threatening circumstance in which the walls of the aorta weaken and begin to separate. The most significant risk of atherosclerosis, however, is HEART ATTACK or STROKE, resulting from particles of atherosclerotic plaque that break free and become lodged in an artery. The blockage may occur at the location of the occlusion or at a distant site. Blood clots also may form at the sites of the plaque accumulations (atheromas), occluding the artery at the site or, like the plaque particles, breaking free and becoming lodged elsewhere in the body.

Symptoms and Diagnostic Path

Atherosclerosis typically does not present symptoms until it advances to a further disease state such as CAD or hypertension resulting from renal artery stenosis. A key indicator that atherosclerosis exists, however, is elevated blood lipid (cholesterol and triglycerides) levels. Cardiologists generally perceive a total blood cholesterol level of 200 as indicating that there is some degree of atherosclerotic disease present. Lowering CHOLESTEROL BLOOD LEVELS reduces the risk for further atherosclerotic deposits and can also reverse to some extent atherosclerotic disease that already exists. The diag-

nostic path typically includes CARDIAC CATHERIZATION or vascular catheterization, which allows the cardiologist to directly visualize the extent of atherosclerotic disease present. ELECTRON BEAM COMPUTED TOMOGRAPHY (EBCT) SCAN, a noninvasive imaging procedure, shows promise for identifying atherosclerosis in its early stages. EBCT detects calcium in the atherosclerotic deposits.

Treatment Options and Outlook

Treatment may target the damaged arteries, the underlying disease process, or both. Treating the damaged artery generally takes precedence as the atherosclerotic occlusions restrict and may even block the flow of blood.

Risk Factors and Preventive Measures

The primary risk factor for atherosclerosis is elevated cholesterol blood levels, which allow fatty acids to accumulate in the blood. Cigarette smoking, OBESITY, hypertension, and DIABETES further increase the risk for atherosclerosis. Cigarette smoking and hypertension alter the cells of the arterial walls in ways that reduce their FLEXIBILITY, making them more susceptible to atherosclerotic accumulations. Diabetes and obesity both alter lipid METABOLISM. Preventive measures include a diet with fewer than 10 percent of its CALORIES from saturated fats (such as meats), daily physical exercise, SMOKING CESSATION, and WEIGHT LOSS AND WEIGHT MANAGEMENT. Health experts encourage people to develop heart-healthy lifestyle habits early in life, as so much research now confirms that the cardiovascular diseases common in people who are in their 60s and beyond get their start in the teenage years or earlier.

See also CALORIE; CARDIOVASCULAR DISEASE PREVENTION; DIET AND HEALTH; EXERCISE AND HEALTH; LIFESTYLE AND CARDIOVASCULAR HEALTH; PHYSICAL EXERCISE AND CARDIOVASCULAR HEALTH; PULMONARY EMBOLISM.

atherosclerotic plaque Debris that collects within the inner layer of the wall of an artery, also called arterial plaque. Atherosclerotic plaque typically includes fatty acids, dead cells, platelets, and other particles such as proteins and minerals (notably calcium, which gives the plaque its stiffness). The fatty acids, such as cholesterol and triglycerides, are heavy and sticky. The flow of the BLOOD pushes them to the outer edges, up against the arterial walls. Initially the debris is a minor irritation to the inner surface of the arteries. Over time, however, the irritation creates INFLAMMATION that attracts further debris. The sticky nature of the debris in combination with the inflammation establishes a circumstance in which the debris becomes embedded within the intima, the inner layer of the arterial wall, creating deposits called atheromas and evolving into the disease state of ATHEROSCLEROSIS. Atherosclerotic plaque in the CORONARY ARTERIES becomes CORONARY ARTERY DISEASE (CAD) and in other arteries becomes PERIPHERAL VASCULAR DISEASE (PVD).

See also CAROTID STENOSIS; CHOLESTEROL BLOOD LEVELS; HYPERLIPIDEMIA; LIFESTYLE AND CARDIOVASCULAR HEALTH; PLATELET; TRIGLYCERIDE BLOOD LEVEL.

atrial fibrillation An ARRHYTHMIA in which the upper chambers of the HEART, the atria, contract rapidly and out of synchronization with each other. As a consequence, they do not pump BLOOD very effectively to the ventricles. Though most of the blood that enters the atria drains to the ventricles, some blood pools in the atria. The pooled blood establishes a very high risk for blood clots to form and a corresponding increase in the risk of STROKE or TRANSIENT ISCHEMIC ATTACK (TIA). Atrial fibrillation is the cause of one in five strokes. Atrial fibrillation is the most common arrhythmia that requires treatment, affecting about 5 percent of people over age 65.

The typical symptoms of atrial fibrillation include

- PALPITATIONS
- rapid tiring during physical activity
- generalized fatigue
- DYSPNEA (shortness of breath)
- ANGINA PECTORIS (CHEST PAIN)
- SYNCOPE (fainting)

However, many people have mild or no symptoms, with the doctor detecting atrial fibrillation during the course of examination for other health concerns.

HYPOTENSION (low BLOOD PRESSURE) and a weak, irregular, and often rapid PULSE are common signs

the doctor detects during examination. An ELECTROCARDIOGRAM (ECG) confirms the diagnosis. ECHOCARDIOGRAM may reveal the underlying cause of the arrhythmia, especially when VALVULAR HEART DISEASE is to blame. Antiarrhythmia medications such as beta blockers or calcium channel blockers restore a normal heart rhythm (normal sinus rhythm) in most people who have atrial fibrillation. These medications can have mild to significant side effects and can slow the heart too much, causing bradycardia, another arrhythmia.

For atrial fibrillation that does not respond to these medical measures, the cardiologist may suggest CARDIOVERSION, which uses electrical shock to jolt the heart back into normal rhythm, or RADIOFREQUENCY ABLATION, which destroys a small portion of heart tissue to permanently disrupt the flow of electrical impulses in the heart. Cardiologists typically prescribe ANTICOAGULATION THERAPY, usually aspirin or warfarin and sometimes both, in addition to antiarrhythmia medications for people who have atrial fibrillation, to reduce the risk for clot formation and resulting stroke.

Common causes of atrial fibrillation include HYPERTENSION (high blood pressure), CORONARY ARTERY DISEASE (CAD), congestive HEART FAILURE, PERICARDITIS, and RHEUMATIC HEART DISEASE. Atrial fibrillation may follow MYOCARDIAL INFARCTION and is also more common among people who have DIABETES or HYPERTHYROIDISM. There are no known measures for preventing atrial fibrillation beyond lifestyle behaviors to maintain overall cardiovascular health.

See also GALLOP; LIFESTYLE AND CARDIOVASCULAR HEALTH; LONG QT SYNDROME (LQTS); MEDICATIONS TO TREAT CARDIOVASCULAR DISEASE; WOLFF-PARKINSON-WHITE SYNDROME.

atrioventricular (AV) node A cluster of electrical fibers in the HEART that focuses and intensifies the electrical impulses the SINOATRIAL (SA) NODE initiates. The SA node, a cluster of specialized NERVE fibers at the top of the right atrium near the superior VENA CAVA, is the heart's natural PACEMAKER. It generates a rhythmic electrical impulse that spreads through the myocardial cells of the right atrium. The AV node, located at the base of the right atrium at its juncture with the right ventricle, gathers the impulse and amplifies it, sending it through the BUNDLE OF HIS and into the right and left bundle branches. The electrical impulse gathers STRENGTH as it travels these electrical conduits, culminating in the Purkinje fibers near the base of each ventricle. The impulse then cascades through the myocardial cells of the ventricles, bringing the cells and the ventricles to synchronized contraction. The AV node also can generate a pacing impulse when disease or damage to the heart blocks the SA node's impulse, though the AV node impulse is considerably weaker and can sustain limited cardiac function for only a short time.

For further discussion of the AV node within the context of cardiovascular structure and function, please see the overview section "The Cardiovascular System."

See also BUNDLE BRANCH; BUNDLE BRANCH BLOCK; CARDIAC CYCLE; ELECTROCARDIOGRAM (ECG); SICK SINUS SYNDROME.

automated external defibrillator (AED) A portable, computerized device to shock a HEART in fibrillation (rapid, useless contractions) into a functional rhythm. AEDs debuted in the 1990s and now are available in many public locations and workplaces. Older models are the size of a small briefcase; newer models are smaller and lighter, with some designed for transport by rescuers on bicycles or on foot. Though manufacturers and emergency medical response experts recommend people obtain training in their use, the devices are simple enough for anyone to use without training. Most models use a computerized voice to provide step-by-step instructions. Once the rescuer applies the pads to the chest of the person having the HEART ATTACK, the AED automatically reads the electrical activity of the heart and determines whether there is sufficient activity for an electrical shock to be therapeutic. An electrical shock cannot help a heart that has no electrical activity. The AED is preset to deliver a precise level and length of shock. AEDs are also available for home use by people at high risk for life-threatening arrhythmias. Many emergency response courses, including the basic life support curriculum, routinely teach AED use.

See also ARRHYTHMIA; CARDIAC ARREST; CARDIOPULMONARY RESUSCITATION (CPR); CARDIOVERSION; ELECTROCARDIOGRAM (ECG); SUDDEN CARDIAC DEATH.

B

blood pressure The force BLOOD exerts against the walls of the arteries as it travels through them, as a combination of resistance and the HEART's pumping effort. A sphygmomanometer is the device that measures blood pressure, reported in millimeters of mercury (mm Hg). A typical blood pressure reading reports the pressure at the peak (systole, at ventricular contraction) and trough (diastole, at ventricular filling) of the CARDIAC CYCLE. The first number in a blood pressure reading is the systolic measure and the second number is the diastolic measure. These measures are independently important as well as significant in combination. Blood pressure is among the vital signs health-care providers measure to assess general health status.

Several mechanisms within the body, including neurologic actions in the brainstem and hormonal actions initiated in the KIDNEYS, regulate blood pressure. Clusters of specialized NERVE cells in the heart and major arteries, called baroreflex sensors, continuously send biochemical signals to the regulatory mechanisms. These mechanisms are redundant—that is, they overlap one another to respond to physiologic changes such as fluid volume and oxygen demand. These mechanisms increase blood pressure by constricting arteries and arterioles, raising the resistance blood encounters as it flows through these blood vessels, and correspondingly increasing the rate and force of the heart's contractions. They decrease blood pressure through reverse actions, dilating arteries and arterioles and decreasing the heart's pumping force. Blood pressure typically increases with exercise or stress, reflecting increased METABOLISM. Higher blood pressure pushes oxygen and NUTRIENTS more rapidly into the CAPILLARY BEDS, speeding the rate at which these substances reach cells.

Blood pressure that is higher than is optimal for cardiovascular health is HYPERTENSION; blood pressure that is too low to adequately circulate blood is HYPOTENSION. Most hypotension occurs as a SIDE EFFECT of medications or neurologic conditions, although some degree of hypotension is common with cardiovascular slowing in aging. Researchers believe age-related hypotension reflects disturbances of the baroreflexes. Cardiologists may prescribe medications to constrict the arteries and intensify the heart's contractions when hypotension causes symptoms such as mental confusion or SYNCOPE (fainting).

BLOOD PRESSURE VALUES

Classification	Systolic	Diastolic
healthy	below 120 mm Hg	below 80 mm Hg
prehypertension	120–139 mm Hg	80–89 mm Hg
stage 1 hypertension	140–159 mm Hg	90–99 mm Hg
stage 2 hypertension	160 mm Hg and above	100 mm Hg and above

Hypertension poses a significant threat to cardiovascular health, raising the risk for HEART ATTACK, RENAL FAILURE, and STROKE. Researchers do not fully understand how hypertension develops, though they do know the contributing factors the development of it (salt intake, physical inactivity, OBESITY, and DIABETES) as well as how to influence blood pressure regulatory mechanisms to bring it under control in most situations. Hypertension exists when either systolic or diastolic pressure is elevated. Health conditions that contribute to hypertension include

- arteriosclerosis, atherosclerotic disease, and cigarette smoking, each of which stiffens the arteries and narrows the arterioles

- diabetes, which damages the blood vessels, particularly the smaller arteries and the arterioles
- OBESITY, which increases body mass and creates additional pressure against the blood vessels

Health experts recommend reduced salt consumption, WEIGHT LOSS AND WEIGHT MANAGEMENT, daily physical exercise, and no smoking to maintain optimal blood pressure. Many people who have hypertension also are on ASPIRIN THERAPY or ANTICOAGULATION THERAPY to reduce their risk for heart attack and stroke.

See also ARTERY; EXERCISE AND HEALTH; LIFESTYLE AND CARDIOVASCULAR HEALTH.

body shape and cardiovascular health Although OBESITY in general raises the risk for numerous health conditions, the distribution pattern of excess body fat correlates to the level of risk for CARDIOVASCULAR DISEASE (CVD) as well as other health conditions such as DIABETES. Numerous research studies affirm that people who carry excess body fat primarily around the waist, the "apple" or "fat tire" body shape, are three times more likely to develop cardiovascular conditions such as HYPERTENSION (high BLOOD PRESSURE), ATHEROSCLEROSIS, CORONARY ARTERY DISEASE (CAD), ISCHEMIC HEART DISEASE (IHD), and PERIPHERAL VASCULAR DISEASE (PVD).

WAIST AND HIP MEASUREMENTS

To measure the waist:

1. Breathe out.
2. Place a measuring tape (or piece of string) snugly but not cinched around the waist, between the crest of the hip bones and the navel (belly button).
3. Note the measurement (or use a ruler to measure the string).

To measure the hips:

1. Place a measuring tape (or piece of string) snugly but not cinched around the hips at their widest point.
2. Note the measurement (or use a ruler to measure the string).

Researchers believe the "apple" pattern of body fat distribution reflects a higher level of INSULIN RESISTANCE than the "pear" body shape in which the body stores excess fat in the hips, thighs, and more equitably throughout the body. This is significant because INSULIN plays a key role in LIPID METABOLISM and regulating blood levels of cholesterol and triglycerides. Excesses of these lipids (HYPERLIPIDEMIA) lead to atherosclerosis, the accumulation of deposits in the inner layer of the walls of the arteries. Atherosclerosis is the foundation of occlusive cardiovascular conditions such as CAD and PVD, and the cause of some types of hypertension (namely renal vascular hypertension).

The WAIST-TO-HIP RATIO (WHR), which is the WAIST CIRCUMFERENCE divided by the hip circumference, determines a person's body shape classification. A WHR greater than 0.9 in men or 0.8 in women defines a body shape as "apple." Maintaining a healthy weight and daily physical exercise are especially important for people who have "apple" body shapes. Exercise improves INSULIN sensitivity and helps keep blood lipid levels and blood pressure within healthy ranges. In turn, this reduces the risk for diabetes as well as cardiovascular disease.

See also ABDOMINAL ADIPOSITY; EXERCISE AND HEALTH; LIFESTYLE AND CARDIOVASCULAR HEALTH; WEIGHT LOSS AND WEIGHT MANAGEMENT.

bundle branch An organization of NERVE fibers along the heart's ventricular septum that conveys electrical impulses to the ventricles to cause them to contract, also called the BUNDLE OF HIS. The right bundle branch extends to the right ventricle and the left bundle branch to the left ventricle. The electrical impulses, which originate with the SINOATRIAL (SA) NODE, intensify as they travel along the bundle branches. The bundle branches, as the name implies, branch out into smaller and smaller fibers culminating in the Purkinje fibers, which disperse the electrical impulses to the myocardial cells throughout the ventricles.

For further discussion of the bundle branches within the context of cardiovascular structure and function, please see the overview section "The Cardiovascular System."

See also ATRIOVENTRICULAR (AV) NODE; BUNDLE BRANCH BLOCK; ELECTROCARDIOGRAM (ECG); HEART.

bundle branch block An impediment, partial or complete, that prevents electrical impulses from

traveling along the BUNDLE OF HIS or one of the bundle branches, right or left, in the HEART. The bundle branches focus and intensify the pacing signals that originate in the SINOATRIAL (SA) NODE, concentrating them enough to stimulate and synchronize the powerful contractions the ventricles need to eject BLOOD from the heart. Various factors can block this electrical pathway. Among the most common are CORONARY ARTERY DISEASE (CAD), VALVULAR HEART DISEASE, HEART FAILURE, and CARDIOMYOPATHY. These conditions result in abnormal blood supply to the myocardial cells, interfering with their normal functions. BUNDLE BRANCH block also can exist without an identifiable cause in people who have no apparent heart disease.

Bundle branch block typically shows up on an ELECTROCARDIOGRAM (ECG) though often does not cause symptoms. The heart continues to contract and pump blood normally (unless other heart disease interferes) because factors other than electrical stimulation contribute to heart function. However, the slowed, delayed, or interrupted flow of the electrical pacing impulse can cause a slow heart rate (bradycardia) or other types of ARRHYTHMIA. The location of the blockage can disrupt the synchronized contractions of the ventricles, causing one to contract before the other instead of both contracting simultaneously. Often, the bundle branch block requires only regular monitoring, not treatment. The location and extent of the block determines the approach. When the block is fairly extensive, a PACEMAKER may be necessary to regulate the heart's electrical activity. Bundle branch block that coexists with other forms of heart disease may require careful coordination of therapeutic measures to preserve overall cardiac function to the greatest extent possible.

See also SICK SINUS SYNDROME.

bundle of His The bundle of NERVE fibers that conveys the heart's electrical pacing impulse from the ATRIOVENTRICULAR (AV) NODE to the ventricles, also called the bundle branches. The short trunk portion of the bundle before it splits into the right BUNDLE BRANCH (right bundle of His) and left bundle branch (left bundle of His) is the main bundle of His. The German physician Wilhelm His (1863–1934) discovered the bundle branches in 1893. Doctors may use the terms bundle of His and bundle branch interchangeably.

For further discussion of the bundle of His within the context of cardiovascular structure and function, please see the overview section "The Cardiovascular System."

See also ARRHYTHMIA; BUNDLE BRANCH BLOCK; HEART; SICK SINUS SYNDROME.

C

capillary beds The meshlike network of arterioles and venules, the body's tiniest BLOOD vessels, where OXYGEN–CARBON DIOXIDE EXCHANGE takes place. Arterial pressure forces blood into the capillary beds. Erythrocytes (red blood cells) carry oxygen and other NUTRIENTS to the capillary beds, where these molecules pass through to cells. Correspondingly, the cells pass metabolic waste such as CARBON DIOXIDE and lactic acid through to the blood. The arterioles and the venules intertwine in the capillary beds, becoming indistinguishable. Capillary beds are present throughout the body.

For further discussion of the capillary beds within the context of cardiovascular structure and function, please see the overview section "The Cardiovascular System."

See also ARTERY; ERYTHROCYTE; LUNGS; VEIN.

cardiac arrest Cessation of the heart's contractions. Cardiac arrest may occur as the result of arrhythmias (irregularities in the heartbeat), MYOCARDIAL INFARCTION (clot that blocks the flow of BLOOD through the CORONARY ARTERIES to the HEART MUSCLE), HYPOXIA (such as in drowning), ELECTROCUTION, COCAINE use, or blunt trauma to the chest. Without immediate resuscitative efforts to restore heartbeat, OXYGENATION, and circulation, death occurs within minutes. About 350,000 Americans die of cardiac arrest each year.

Although cardiac arrest can follow HEART ATTACK, they are not the same event. Cardiac arrest typically occurs suddenly and with few warning indications. People at highest risk for cardiac arrest are those who have disorders of the heart's electrical system such as LONG QT SYNDROME (LQTS), SICK SINUS SYNDROME, BUNDLE BRANCH BLOCK, WOLFF-PARKINSON-WHITE SYNDROME, and ventricular arrhythmias.

More than half of cardiac arrests occur in people who do not know they have CARDIOVASCULAR DISEASE. Most cardiac arrests take place at home with no one witnessing the event. By the time someone finds the person who has had cardiac arrest, often it is too late for resuscitation to succeed. Health experts believe prompt resuscitation could save 70 to 80 percent of people who experience cardiac arrest. CARDIOPULMONARY RESUSCITATION (CPR) is most effective within four minutes of the onset of cardiac arrest. Automated external defibrillators (AEDs), small computerized devices that automatically read the heart's rhythm and can administer a jolt of electricity to shock the heart into a functional rhythm, have become more common in public locations and at workplaces. AEDs have saved numerous lives of people who have had cardiac arrests.

See also ARRHYTHMIA; AUTOMATED EXTERNAL DEFIBRILLATOR (AED); CARDIOPULMONARY RESUSCITATION (CPR); SUDDEN CARDIAC DEATH.

cardiac capacity The ability of the HEART to increase CARDIAC OUTPUT to meet the body's increased needs for oxygen during physical activity or exercise. Cardiac capacity is a combination of the heart's physical condition and the body's AEROBIC FITNESS level. Damage to the heart, such as may occur with MYOCARDIAL INFARCTION and ISCHEMIC HEART DISEASE (IHD), reduces cardiac capacity, as do conditions that weaken the heart MUSCLE such as CARDIOMYOPATHY and HEART FAILURE. Cardiac capacity also diminishes as a normal dimension of aging. Aerobic conditioning through consistent, moderate to intense, AEROBIC EXERCISE improves cardiac capacity and helps sustain cardiovascular health.

See also AEROBIC CAPACITY; AEROBIC EXERCISE; AGING, CARDIOVASCULAR CHANGES THAT OCCUR WITH; PHYSICAL EXERCISE AND CARDIOVASCULAR HEALTH.

cardiac catheterization A diagnostic or therapeutic procedure in which the cardiologist inserts a long, flexible, thin tube into an ARTERY near the surface of the SKIN and threads it through the artery into the HEART or the CORONARY ARTERIES. The cardiologist uses FLUOROSCOPY (moving X-RAY) to view the progress of the catheter's insertion via closed-circuit television. During cardiac catheterization the cardiologist typically injects dye into the coronary arteries to visualize the flow of BLOOD through them (cardiac ANGIOGRAM).

Reasons for Doing This Test

Cardiac catheterization helps diagnose CORONARY ARTERY DISEASE (CAD) and the extent of coronary artery occlusion (blockage). The cardiologist also may use cardiac catheterization to diagnose damaged or dysfunctional heart valves and biopsy the endomyocardium (inner lining and MYOCARDIUM of the heart). Therapeutic applications of cardiac catheterization include ATHERECTOMY and percutaneous transluminal coronary angioplasty (PCTA), also called balloon ANGIOPLASTY. In PCTA the cardiologist inflates a tiny balloon at the catheter's tip to compress ATHEROSCLEROTIC PLAQUE that is occluding a coronary artery.

Preparation, Procedure, and Recovery

Cardiac catheterization requires little preparation beyond nothing to eat or drink for six to eight hours before the scheduled procedure. The catheterization takes place in a sterile setting. Because there is a slight risk for complications that would require immediate OPEN HEART SURGERY, the catheterization facility has full operating room and surgical team capacity. At the start of the procedure the cardiologist administers a general sedative to help the person relax, and injects a local anesthetic into the tissues around the area where the catheter will enter the artery. The cardiologist makes a tiny incision to gain entrance to the artery, and threads the catheter through the artery to the heart and coronary arteries. Typically the cardiologist videotapes the catheterization for further study or review following the procedure.

Depending on the reason for the catheterization and the cardiologist's findings, the procedure takes 45 to 90 minutes. When finished, the cardiologist withdraws the catheter, sutures the insertion incision, and places a pressure dressing over the wound. The person remains lying down for six to eight hours, in a recovery area, allowing a good clot formation to develop and also permitting the sedative to wear off. Most people are able to go home the same day, though must have a friend or relative do the driving, and can return to regular activities within a week.

Risks and Complications

The most significant, though an uncommon, risk of cardiac catheterization is HEART ATTACK or STROKE from atherosclerotic plaque the catheter dislodges. Some people may have a HYPERSENSITIVITY REACTION or allergic response to the injected dye with angiogram. Also uncommon—though possible—is that the cardiologist may discover, upon reaching the occlusion, that the atheroma (plaque formation) is unstable and may determine that immediate CORONARY ARTERY BYPASS GRAFT (CABG) will be necessary. More common complications include bleeding and discomfort at the insertion site or INFECTION after the procedure. For most people, cardiac catheterization is uneventful and provides the information the cardiologist needs to make a definitive diagnosis.

See also STENT; SURGERY BENEFIT AND RISK ASSESSMENT; VALVULAR HEART DISEASE.

cardiac cycle The complete sequence of the heart's contractions that results in ejecting BLOOD from the HEART to the LUNGS and body. Each cardiac cycle represents two paired actions that begin when the SINOATRIAL (SA) NODE, a cluster of specialized NERVE cells located at the apex of the right atrium, emits an electrical pacing impulse. The impulse causes the right and left atria to contract simultaneously, sending blood to the respective ventricles. The right atrium sends to the right ventricle deoxygenated blood returning to the heart from the body; the left atrium sends to the left ventricle oxygenated blood returning to the heart from the lungs.

The ATRIOVENTRICULAR (AV) NODE, a second cluster of specialized nerve cells located at the base of

the right atrium, initiates the second phase of the cardiac cycle. The AV node picks up, amplifies, and focuses the electrical impulse that has passed through the atria, sending it along the BUNDLE OF HIS and the bundle branches in wavelike fashion. The impulse causes the ventricles to contract simultaneously. The right ventricle pumps blood to the lungs for OXYGENATION, and the left ventricle pumps oxygenated blood into the AORTA for the arterial network to carry through the body.

The PULSE represents a completed cardiac cycle. The heart of an adult at rest completes about 80 cardiac cycles each minute. ARRHYTHMIA, VALVULAR HEART DISEASE, CORONARY ARTERY DISEASE (CAD), ISCHEMIC HEART DISEASE (IHD), congenital defects of the heart, and damage to the heart such as occurs with HEART FAILURE or HEART ATTACK are among the conditions that can disrupt the cardiac cycle.

See also BLOOD PRESSURE; BUNDLE BRANCH; CONGENITAL HEART DISEASE; SICK SINUS SYNDROME.

cardiac enzymes Proteins the HEART releases into the bloodstream when HEART ATTACK or other circumstances cause damage to the heart MUSCLE (MYOCARDIUM). BLOOD tests that measure the levels of these enzymes help doctors determine whether, and how long ago, a heart attack has taken place. All muscle tissue releases certain enzymes when injured, so the combination of enzymes present in the blood provides the most useful clues as to the source of the injury. The cardiac-specific enzymes that indicate heart attack are cardiac troponin-T and cardiac troponin-I. The levels of these enzymes in the blood rise 3 to 6 hours after damage to the heart and remain elevated for 7 to 10 days.

Nonspecific enzymes that may suggest heart attack include creatine kinase (CK), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH). Elevations of these enzymes occur whenever there is significant damage to muscle tissue of any kind. To cardiologists determining whether a person has had a heart attack, it is the rise and fall of the enzyme levels that are more useful than the levels themselves at any one point in time. Creatine kinase MB (CK-MB), one of the protein components of creatine kinase, rises more rapidly and dramatically when the damage is to heart muscle, providing a strongly suggestive marker. CK-MB rises within a few hours of heart damage though returns to normal in about 24 hours. Cardiologists evaluate cardiac enzyme levels in combination with other clinical evidence such as ELECTROCARDIOGRAM (ECG) and ECHOCARDIOGRAM to confirm the diagnosis of MYOCARDIAL INFARCTION (death of heart muscle cells due to lack of oxygen).

See also CARDIAC CATHETERIZATION.

cardiac intensive care unit (CICU) A specialized unit within a hospital that provides comprehensive medical care for people recovering from HEART ATTACK or receiving treatment for other life-threatening cardiovascular diseases. Large hospitals have separate units for medical patients (such as those who have had HEART attacks but not surgery) and surgical patients (such as those who have had CORONARY ARTERY BYPASS GRAFT (CABG), heart valve replacement, or other operations on the heart); in smaller hospitals a single specialized unit provides care for both kinds of patients. The nurses and ancillary health-care staff who work in CICUs have specialized training in using the monitoring equipment and caring for patients who have serious cardiovascular conditions. Most CICUs restrict visitors and visiting times to protect patients and allow them to receive adequate rest as well as the intensive nursing care their conditions require.

See also CARDIAC REHABILITATION; HEART TRANSPLANTATION; MECHANICAL VENTILATION.

cardiac output The volume of BLOOD the HEART pumps out to the body each minute. Cardiac output is an important measure of the heart's efficiency. Many cardiovascular diseases, such as ARRHYTHMIA and HEART FAILURE, can limit cardiac output. Cardiologists measure cardiac output as the combination of HEART RATE and stroke volume (the amount of blood the left ventricle ejects into the AORTA with each contraction). There are several methods for determining stroke volume, including dye injection and thermal differential.

In a person whose cardiovascular system is healthy, cardiac output increases with increased physical activity such as exercise, in which both heart rate and the force of the heart's contractions increase. A heart with damage due to disease such as CARDIOMYOPATHY or HEART FAILURE, or as a conse-

quence of MYOCARDIAL INFARCTION, cannot increase the force of its contractions, limiting cardiac output. Severe damage can result in cardiac output that is less than the body's needs even at rest. Medications to strengthen the heart and focus the efforts of its contractions can often improve cardiac efficiency, though only mediating the underlying cause can restore adequate cardiac output.

People who have a high AEROBIC FITNESS level, such as athletes and those who regularly engage in AEROBIC EXERCISE, can significantly increase their cardiac output to send more blood to their muscles. During intense aerobic activity, 60 percent or more of the cardiac output may go to the skeletal muscles. High cardiac output is essential to get enough blood and oxygen to vital organs at the same time.

See also CARDIAC CAPACITY; LEFT VENTRICULAR EJECTION FRACTION (LVEF).

cardiac rehabilitation Planned activities, course of recovery, or structured program for improving cardiovascular health after HEART ATTACK, CORONARY ARTERY BYPASS GRAFT (CABG), HEART TRANSPLANTATION, and other major cardiovascular events or operations. Many people, after such events, need to make significant lifestyle changes. A structured cardiac rehabilitation program helps people to define their needs and goals and establish realistic steps to move progressively toward meeting them. Most people benefit from assistance with meal planning and nutrition, exercise, and SMOKING CESSATION. Structured programs also offer social interaction with other people who have similar experiences, and may include organized SUPPORT GROUPS for people to share their feelings, perceptions, and suggestions.

Many factors influence a person's ability to participate in physical activity. Many hospitals and medical centers offer physician-supervised cardiac rehabilitation programs that feature defined yet individualized activities, some of which may take place at a facility such as a rehabilitation center and others designed for the person to do at home. Some medically supervised cardiac rehabilitation programs incorporate ambulatory ELECTROCARDIOGRAM (ECG) so people can use the telephone to send their ECG readings to cardiologists who can then determine whether physical exercise is within therapeutic range and provide assurance that the HEART is functioning satisfactorily.

Programs such as those health clubs and organizations such as the YMCA offer are less comprehensive and not under a physician's direction. They primarily provide classes in aerobic and resistance exercises as well as access to facilities and equipment. A nutritional counselor separately provides dietary guidance including instruction for WEIGHT LOSS AND WEIGHT MANAGEMENT. People who have health conditions other than cardiovascular, such as DIABETES or chronic OSTEOARTHRITIS, may need additional consultations or professional guidance to accommodate all of their health needs.

Current medical practice emphasizes a return to regular activities as quickly as possible following heart attack or major heart surgery. This reduces the risk of BLOOD clots that can cause STROKE, another heart attack, or PULMONARY EMBOLISM (blood clot in the LUNG). It also expedites HEALING and counters the emotional swings, especially DEPRESSION and anxiety, that are common with serious CARDIOVASCULAR DISEASE (CVD). Research studies have conclusively demonstrated that people who engage in cardiac rehabilitation and maintain heart-healthy lifestyle changes are much less likely to experience additional cardiovascular events and may even halt or reverse cardiovascular conditions such as ATHEROSCLEROSIS and HYPERTENSION (high BLOOD PRESSURE).

BENEFITS OF CARDIAC REHABILITATION

decreased CHOLESTEROL BLOOD LEVELS	faster return to work and other activities
fewer cardiovascular symptoms	improved AEROBIC FITNESS
improved ATHEROSCLEROSIS	improved INSULIN sensitivity
improved nutritious eating habits	improved QUALITY OF LIFE
lowered BLOOD PRESSURE	reduced postoperative discomfort
reduced risk of health problems related to smoking	stress reduction
WEIGHT LOSS AND WEIGHT MANAGEMENT	

Heart attack or major heart surgery is a significant trauma for an individual to experience, with both physical and emotional components. Many people are fearful about the level of physical activity their bodies, and especially hearts, can tolerate. Some people respond with reluctance to do anything and others leap into action with a fervor

that would challenge even someone in peak cardiovascular function. Neither extreme is healthy and can result in further health problems. A person who has not been physically active for years to decades often benefits from the advice and suggestions of a health expert who can help determine an appropriate entry point for returning to an active lifestyle.

Recent studies affirm that cardiac rehabilitation has therapeutic value for people who have chronic cardiovascular conditions such as congestive HEART FAILURE, improving symptoms and QUALITY OF LIFE. Many people will begin cardiac rehabilitation before leaving the hospital after treatment or surgery, starting with an exercise STRESS TEST to determine cardiopulmonary capacity, and continue in a structured way for 3 to 6 months. Under ideal circumstances the activities of rehabilitation, including EATING HABITS and nutrition, become elements of routine daily living and foster a lifestyle that supports cardiovascular health.

See also DIET AND HEALTH; EXERCISE AND HEALTH; LIFESTYLE AND CARDIOVASCULAR HEALTH; NUTRITIONAL ASSESSMENT; NUTRITIONAL NEEDS; PHYSICAL EXERCISE AND CARDIOVASCULAR HEALTH; SEXUAL ACTIVITY AND CARDIOVASCULAR DISEASE.

cardiac resynchronization therapy (CRT) A method of biventricular pacing in which an implanted device regulates and coordinates the contractions of both ventricles, typically to treat severe HEART FAILURE. SUDDEN CARDIAC DEATH as a result of ARRHYTHMIA is a significant risk in HEART failure, particularly heart failure resulting from dilated CARDIOMYOPATHY. Certain BUNDLE BRANCH BLOCK arrhythmias also benefit from CRT.

Conventional pacing therapy stimulates only the right ventricle, which in an otherwise healthy heart results in contraction of both ventricles as the electrical impulse spreads simultaneously across them. In severe heart failure, however, both ventricles are extensively damaged and do not function in synchronization. Conventional pacing therapy ends up being counterproductive by further extending the dysfunction between the two ventricles. A biventricular PACEMAKER has two leads (wires that conduct electrical impulses), one of which the cardiologist inserts in each ventricle. The pacemaker's discharge sends impulses simultaneously to each lead.

The risks of CRT are similar to those of conventional pacing therapy and include possible INFECTION or blood clots from the inserted leads. These risks are minimal, however, and CRT provides substantial benefit for people whose arrhythmias due to heart failure do not respond to other treatments.

See also IMPLANTABLE CARDIOVERTER DEFIBRILLATOR.

cardiomyopathy Weakness and loss of pumping effectiveness of the HEART, usually with changes to the structure of the heart and in particular the left ventricle. Cardiomyopathy is as likely to affect people under age 40 as people over age 60 and is a leading cause of HEART FAILURE resulting in HEART TRANSPLANTATION. Genetic factors can play a role in cardiomyopathy, especially in younger people, though lifestyle factors such as nutrition and ALCOHOL consumption are also significant. Viral and bacterial infections of the heart (MYOCARDITITIS) can leave the heart MUSCLE damaged. In many situations, however, doctors do not know what causes the structural and functional changes in myocardial (heart muscle) cells that result in primary cardiomyopathy. Secondary cardiomyopathy may also develop as a consequence of other CARDIOVASCULAR DISEASE (CVD), such as ISCHEMIC HEART DISEASE (IHD) and HYPERTENSION (high BLOOD PRESSURE).

The five major types of cardiomyopathy are

- **Dilated cardiomyopathy,** in which the heart enlarges in an attempt to compensate for damage to myocardial cells that limits the heart's ability to efficiently pump BLOOD. Long-term ALCOHOL abuse accounts for the dilated cardiomyopathy in about a third of the people who develop it. Deficiency of vitamin B_1 also damages the heart. Though uncommon in the general US population, vitamin B_1 deficiency can occur with long-term, heavy alcohol consumption as well as with long-term EATING DISORDERS such as anorexia nervosa. Dilated cardiomyopathy is more common in people over age 60.
- **Hypertrophic cardiomyopathy,** in which the walls of the heart, particularly the ventricles, thicken. Some doctors may refer to this

condition as hypertrophic obstructive cardiomyopathy (HOCM) or idiopathic hypertrophic subaortic stenosis (IHSS), both of which are older terms. Hypertrophic cardiomyopathy is hereditary, the result of mutations in a number of genes that regulate proteins essential for myocardial cell contractions (notably myosin, troponin T, and alpha tropomyosin). The hypertrophy, or thickening, typically affects the left ventricle most extensively and can involve the ventricular septum to the extent that the hypertrophy creates an obstruction for the proper functioning of the aortic valve (AORTIC STENOSIS). Undiagnosed hypertrophic cardiomyopathy is a leading cause of SUDDEN CARDIAC DEATH in younger people, especially athletes.

- **Ischemic cardiomyopathy,** which develops secondary to longstanding IHD or following extensive or repeated MYOCARDIAL INFARCTION. Ischemia results from inadequate oxygen supply to the cells, some of which die. The patches of dead muscle tissue do not contract, diminishing the heart's effectiveness. Ischemic cardiomyopathy is more common in people over age 60 who have other forms of cardiovascular disease.
- **Peripartum cardiomyopathy,** which develops in a woman during late PREGNANCY or in the first few months after CHILDBIRTH. It appears an inflammatory process in the body, though doctors are uncertain what sets it off. In some situations there is a clear bacterial or viral INFECTION, but most often there is no apparent reason for the INFLAMMATION. Most women fully recover from peripartum cardiomyopathy though are at increased risk for developing it again with subsequent pregnancies.
- **Restrictive cardiomyopathy,** in which the myocardial cells accumulate deposits that cause them to lose elasticity. The loss restricts the ability of the heart to expand, reducing the ability of the ventricles to properly fill with blood. As a consequence, the heart cannot pump enough blood to meet the body's needs. Restrictive cardiomyopathy is secondary to other health conditions such as AMYLOIDOSIS, which leaves protein deposits, and HEMACHROMATOSIS, which leaves iron deposits.

Symptoms and Diagnostic Path

Cardiomyopathy often does not show symptoms until the condition is quite advanced, and then the symptoms are likely to be those of other cardiovascular conditions, such as hypertension and heart failure, especially congestive heart failure. Doctors commonly discover cardiomyopathy during chest X-RAY done for other reasons. When symptoms are present, they typically include

- shortness of breath (DYSPNEA)
- weakness and tiredness
- inability to participate in physical activities

The diagnostic path includes ELECTROCARDIOGRAM (ECG), which detects the arrhythmias typical of an overworked heart, and ECHOCARDIOGRAM, which shows the heart's enlargement and altered function. These tests can provide definitive diagnosis for most cardiomyopathy. Other diagnostic procedures the cardiologist may recommend, depending on the kind of cardiomyopathy suspected, may include COMPUTED TOMOGRAPHY (CT) SCAN, MAGNETIC RESONANCE IMAGING (MRI), transesophageal echocardiogram (TEE), angiogram, and myocardial biopsy. GENETIC TESTING to detect mutations commonly associated with hypertrophic cardiomyopathy can help detect the potential for this condition before it manifests symptoms, allowing prophylactic interventions to delay or minimize its development.

Treatment Options and Outlook

All forms of cardiomyopathy make it difficult for the heart to pump blood effectively. Though in the early stages of the condition the heart's enlargement can compensate for some of the diminished STRENGTH, eventually the compensatory measures become ineffective and even counterproductive. Treatment targets improving the heart's efficiency, usually through a combination of medications and lifestyle modifications. Medications typically include diuretics to reduce edema (fluid accumulations), antiarrhythmia medications to maintain the heart's regular rhythm, vasodilator medications to relax the blood vessels and reduce resistance for blood flow, and medications such as digoxin (inotropic medications) to strengthen the heart's pumping effectiveness. It also is crucial to

treat any coexisting or causative cardiovascular disease such as hypertension, ATHEROSCLEROSIS, and CORONARY ARTERY DISEASE (CAD). Such measures allow the majority of people who have cardiomyopathy, particularly dilative cardiomyopathy, to enjoy normal lives.

Progressive cardiomyopathy necessitates substantial lifestyle changes and is a leading cause of disability due to cardiovascular disease. Hypertrophic, ischemic, and restrictive cardiomyopathies are most likely to be progressive. The therapeutic approach is to manage symptoms to the extent possible, making lifestyle adaptations such as reduced physical activity to accommodate diminished CARDIAC CAPACITY. Heart transplantation becomes a treatment option for people under age 65 who are otherwise healthy. Cardiomyopathy accounts for about half of heart transplantations performed in the United States. In some situations an implanted ventricular assist device (VAD) can supplement the natural heart's function, allowing the heart to regain strength and recover from damage. A VAD also can serve as a "bridge" to support the heart while a person waits for a donor heart for transplantation. Sometimes other surgical approaches, such as removing a segment of diseased heart tissue to reduce the size of the ventricle, are successful in restoring the heart's functional ability.

Risk Factors and Preventive Measures

The leading risk factors for most forms of cardiomyopathy are physical inactivity and suboptimal nutrition, which are risk factors for cardiovascular disease in general, as well as excessive alcohol consumption, genetics, and other cardiovascular disease. As with any form of cardiovascular disease, controlling lifestyle factors reduces the risk for the condition. Early GENETIC TESTING can help people who have family history of hypertrophic cardiomyopathy to determine whether they are at risk for this condition and to plan appropriate therapeutic approaches to delay its development. Most people who die suddenly because of hypertrophic cardiomyopathy do not know they have the condition. Keeping chronic cardiovascular conditions such as hypertension and atherosclerosis under control reduces the risk for secondary cardiomyopathy.

See also ALCOHOLISM; ARRHYTHMIA; BACTERIA; CARDIOVASCULAR DISEASE PREVENTION; CONGENITAL HEART DISEASE; LIFESTYLE AND CARDIOVASCULAR HEALTH; MEDICATIONS TO TREAT CARDIOVASCULAR DISEASE; MUTATION; QUALITY OF LIFE; RISK FACTORS FOR CARDIOVASCULAR DISEASE; VENTRICULAR ASSIST DEVICES (VADS); VIRUS.

cardiopulmonary bypass A procedure in which a machine takes over the oxygenation and pumping functions of the LUNGS and HEART, making OPEN HEART SURGERY possible. Cardiopulmonary bypass allows the cardiovascular surgeon to stop the heart to operate on it, using the bypass machine to circulate the BLOOD through the body. Physician and researcher John H. Gibbon Jr. developed the first cardiopulmonary bypass machine during more than two decades of research and experimentation that culminated in its use to repair a congenital malformation in an 18-year-old woman's heart in 1953. Gibbon's design remains the foundation of cardiopulmonary bypass machines in use today.

In cardiopulmonary bypass, the surgeon inserts large catheters (cannulas) into the VENA CAVA and the AORTA, then administers a chemical solution to cause the heart to stop beating (cardioplegia). The cannulas channel blood through the bypass machine, which uses a membrane oxygenator to infuse the blood with oxygen and allow carbon dioxide to diffuse. Large doses of heparin, an anticoagulant medication, keep the blood from clotting, and special filters capture air bubbles. A pump mechanism, commonly roller pumps or centrifugal force, moves the blood through the bypass machine and in circulation through the person's body. The bypass machine also cools the blood during surgery, to reduce oxygen consumption by maintaining the body's METABOLISM at a lower rate, and warms it at the conclusion of surgery to prepare for returning the body to its own cardiovascular circulation. At the conclusion of the OPERATION the surgeon withdraws the cannulas and restores the flow of blood and the heartbeat.

The primary risks of cardiopulmonary bypass are blood clots and air bubbles that can cause embolism (occlusion of a blood vessel), damage to red blood cells (HEMOLYSIS), and systemic inflammatory response (IMMUNE SYSTEM activation). There is much debate about whether microemboli that

slip through filtration can cause damage to the BRAIN and lungs. Some people experience neurologic effects such as cognitive dysfunction, memory difficulties, and mood swings in the months after cardiopulmonary bypass. Cardiopulmonary bypass also can affect lung function. However, for most people the benefit of the operation cardiopulmonary bypass makes possible outweighs the potential risk for these usually transitory side effects. Cardiovascular surgeons continue to explore new techniques that reduce or eliminate the need for cardiopulmonary bypass, including MINIMALLY INVASIVE SURGERY and off-pump procedures though these, too, carry risks.

See also CONGENITAL HEART DISEASE; SURGERY BENEFIT AND RISK ASSESSMENT.

cardiovascular disease (CVD) The collective term for the numerous health conditions of the HEART and BLOOD vessels. Cardiovascular disease (CVD) is the leading cause of death and disability in the United States and in many other developed countries. More than 70 million Americans live with CVD; 10 million of them have sufficient disability that they cannot work or participate in the activities they enjoy. CVD claims over 900,000 lives each year. The most common forms of CVD are HYPERTENSION (high BLOOD PRESSURE), ATHEROSCLEROSIS (occluded arteries), CORONARY ARTERY DISEASE (CAD), and ISCHEMIC HEART DISEASE (IHD). Health experts sometimes refer to CAD and IHD collectively as coronary heart disease (CHD).

Most CVD develops as a consequence of lifestyle factors, though age, gender, and genetic predisposition also contribute. The primary risk factors for CVD are

- cigarette smoking
- OBESITY
- physical inactivity
- DIABETES
- renal (kidney) disease
- being a man under age 50
- age over 50 for men and over 60 for women
- family history of CVD

Acquired CVD is largely preventable through lifestyle practices that incorporate nutritious eating habits, daily physical exercise, and not smoking. These practices are also preventive for health conditions that lead to CVD, such as diabetes and obesity. Other forms of CVD may be hereditary or congenital. Hereditary CVD conditions are the result of GENE mutations. CONGENITAL HEART DISEASE results from structural defects in the heart and its major vessels, such as tetralogy of Fallot, or to blood vessels elsewhere in the body, such as ARTERIOVENOUS MALFORMATION (AVM), that occur during early gestational development and are present at birth.

For further discussion of CVD please see the overview section "The Cardiovascular System."

See also AGING, CARDIOVASCULAR CHANGES THAT OCCUR WITH; LIFESTYLE AND CARDIOVASCULAR HEALTH; PREVENTING CARDIOVASCULAR DISEASE; SMOKING AND CARDIOVASCULAR DISEASE.

cardioversion The application of an electrical shock through the chest wall to the HEART, administered under sedation, to alter the heart's electrical rhythm. The cardiologist performs cardioversion in a hospital setting staffed and equipped to respond to cardiovascular emergencies. There is a slight risk for HEART ATTACK or STROKE. Cardioversion is most commonly a treatment for ARRHYTHMIA such as ATRIAL FIBRILLATION, in which the heart's electrical patterns have gotten out of synchronization in some way. The effect may be permanent, long-lasting, or short term. Some people experience slight SKIN irritation at the site of the electrodes or paddles on the surface of the chest following cardioversion. Because the procedure requires a general sedative, there may also be grogginess for several hours. Most people go home within 4 to 6 hours and return to their usual activities the following day.

See also DEFIBRILLATION; IMPLANTABLE CONVERTER DEFIBRILLATOR (ICD); RADIOFREQUENCY ABLATION.

carotid bruit An abnormal sound characteristic of ATHEROSCLEROSIS that the cardiologist hears through a STETHOSCOPE placed over the carotid ARTERY at the base of the neck. The sound, a murmur that occurs during systole (contraction of the left ventricle), represents turbulence as BLOOD passes through areas of the carotid artery where atheromas (collections of ATHEROSCLEROTIC PLAQUE)

occlude the inner channel of the carotid artery. Carotid bruit is a diagnostic sign that indicates the presence of CAROTID STENOSIS (narrowing of the carotid artery) and increased risk for STROKE.

See also ANGIOGRAM; ENDARTERECTOMY; HEART SOUNDS; STENT.

carotid stenosis Narrowing of the carotid ARTERY in the neck due to ATHEROSCLEROSIS. Often carotid stenosis shows no symptoms until it results in a STROKE. The doctor may detect carotid stenosis during routine physical examination when listening to the carotid arteries with a STETHOSCOPE, which reveals the characteristic murmur sound, CAROTID BRUIT, that indicates the stenosis. ANTICOAGULATION THERAPY, most commonly ASPIRIN THERAPY, helps reduce the risk of clot formation at the site of the stenosis though does not prevent or reduce atherosclerotic accumulations. ENDARTERECTOMY, surgery to remove the occluding atheromas (collections of ATHEROSCLEROTIC PLAQUE) and widen the arterial passage, becomes a viable treatment option when the stenosis reaches 60 or 70 percent. ANGIOGRAM, in which the cardiologist uses dye and X-rays to examine the arteries, helps define the degree of occlusion. Stroke occurs when clot or atheroma fragments break free from the site of the stenosis and travel through the carotid artery to the BRAIN.

See also CARDIOVASCULAR DISEASE PREVENTION; SURGERY BENEFIT AND RISK ASSESSMENT.

chest pain Discomfort that arises from the upper portion of the body. CHEST PAIN can have various causes, many of which are not cardiovascular. Discomfort originating from the HEART is characteristically oppressive in nature, though often not the crushing pressure that is the common perception. As many as 25 percent of people do not experience appreciable pain with HEART ATTACK. Gastrointestinal pain often sends people to the emergency room worried about heart attack, yet nearly a third of people who are having heart attacks delay seeking medical care because they do not believe the symptoms they are experiencing, especially chest pain, are severe enough to be heart attack. Chest pain is unreliable as an indicator of the nature or severity of a health situation.

HEALTH CONDITIONS THAT CAN CAUSE CHEST PAIN

BARRETT'S ESOPHAGUS	COSTOCHONDRITIS
dissecting aortic ANEURYSM	ENDOCARDITIS
GALLBLADDER DISEASE	GASTROESOPHAGEAL REFLUX DISORDER (GERD)
HEPATIC ABSCESS	HIATAL HERNIA
LUNG ABSCESS	MYOCARDITIS
PANCREATITIS	PEPTIC ULCER DISEASE
PERICARDITIS	PNEUMONIA
PLEURISY	rib FRACTURES
PULMONARY EMBOLISM with infarction	STOMACH CANCER

See also CARDIOPULMONARY RESUSCITATION (CPR); CHONDRITIS; COCAINE.

cholesterol blood levels The amounts and forms of cholesterol that are present in the bloodstream, usually measured after 8 to 12 hours of fasting (no food) to accommodate short-term rises that could result from eating. Cholesterol is a sterol, a chemical essential for numerous metabolic functions and necessary for health. Because cholesterol cannot dissolve in the BLOOD, it binds with protein carriers called lipoproteins that suspend it in the blood. Cholesterol becomes a health problem when the amount of cholesterol in the blood cir-

CHOLESTEROL BLOOD LEVELS AND CARDIOVASCULAR HEALTH

Cholesterol	Optimal	Moderate Risk	High Risk
HDL-C	≥ 60 mg/dL	< 40 mg/dL	not applicable
LDL-C	≤ 100 mg/dL*	130–159 mg/dL*	>160 mg/dL
total cholesterol	< 200 mg/dL	200–239 mg/dL	≥ 240 mg/dL

**For people with no other cardiovascular risk factors, LDL-C levels of 100–129 mg/dL is optimal. For people with other cardiovascular risk factors, LDL-C levels of 100–129 mg/dL is nearly optimal/slight risk.*

culation exceeds the body's needs. The excess lipoproteins that transport the cholesterol fall out of suspension and infiltrate the inner lining of the arterial walls, forming ATHEROSCLEROTIC PLAQUE. Health factors that increase the risk of elevated lipoprotein-cholesterol blood levels include OBESITY, DIABETES, and HYPERTENSION.

The LIVER produces most of the cholesterol in the blood circulation, manufacturing this necessary chemical from saturated fats and other dietary NUTRIENTS. Dietary cholesterol is a minor factor in this process. The liver continues to manufacture cholesterol as long as it receives the ingredients, via ingested nutrients, to do so. Cells throughout the body also can synthesize cholesterol to meet their needs. The body stores some excess cholesterol, along with other fatty acids (notably triglycerides), in adipose tissue throughout the body. The body can then withdraw this cholesterol when liver synthesis slows. However, adipose tissue can hold only so much. Remaining excess cholesterol stays in the bloodstream.

The liver manufactures the lipoproteins that carry cholesterol as well as triglycerides and phospholipids (collectively called fatty acids or lipids). Different lipoproteins transport the kinds of fatty acids. Very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) transport some cholesterol and most of the triglycerides. It is the excesses of LDL cholesterol (LDL-C) and VLDL cholesterol (VLDL-C) that create increased cardiovascular health risks. These lipoprotein packages settle out of the blood easily, collecting against the inner walls of the arteries. Over time (typically decades) the lipoproteins, along with other cellular debris that gathers, infiltrates the innermost layer of the arterial wall and forms atherosclerotic plaque. This process is the foundation of ATHEROSCLEROSIS.

High-density lipoprotein (HDL) transports primarily cholesterol. It appears that HDL not only carries cholesterol from the liver but also picks up fragments of cholesterol-bearing LDL and VLDL and returns them to the liver, which disassembles them. Lowering the available lipoproteins in the body reduces the excess circulating in the bloodstream and increases the proportion of HDL cholesterol (HDL-C) to LDL-C/VLDL-C. Cells draw the cholesterol they need from the supply in circulation, helping maintain a healthy balance. Generally, the higher a person's total cholesterol, the higher his or her LDL-C levels.

ADDITIONAL CARDIOVASCULAR RISK FACTORS

age 65 or older	CONGENITAL HEART DISEASE
DIABETES	family history of CARDIOVASCULAR DISEASE (CVD)
female past MENOPAUSE	HEART ATTACK
HYPERTENSION	ISCHEMIC HEART DISEASE (IHD)
male, any age	OBESITY
PERIPHERAL VASCULAR DISEASE (PVD)	physically inactive
smoking	STROKE
TRANSIENT ISCHEMIC ATTACK	

When the body's nutrient intake is in balance, the liver uses up the nutrient components available to manufacture cholesterol and lipoproteins, sending into circulation the levels that the body can use. "Optimal" blood cholesterol values identify this balance, or lipid homeostasis, in which there is no increased cardiovascular risk in most people. Researchers have recently determined the LDL level to be the most significant in people who have other RISK FACTORS FOR CARDIOVASCULAR DISEASE.

Current lipid-lowering treatment recommendations emphasize LDL-C blood values; the recom-

CHOLESTEROL-LOWERING MEDICATION RECOMMENDATIONS

LDL-C Level	Risk Factor Profile	Target LDL-C Level
< 100 mg/dL	CVD + 2 or more CVD risk factors	100 mg/dL
130–160 mg/dL	CVD	100 mg/dL
160–190 mg/dL	2 or more CVD risk factors	130 mg/dL
> 190 mg/dL	no CVD or risk factors	160 mg/dL
190–219 mg/dL	male under age 35	160 mg/dL
190–219 mg/dL	female premenopause	160 mg/dL

mended LDL-C level depends on risk factors for CARDIOVASCULAR DISEASE (CVD). The higher the cardiovascular risk, the lower the recommended LDL-C level.

- Treatment may use lifestyle (diet and exercise) modification alone, which is effective for meeting LDL-C target levels for many people whose LDL-C blood values are 100–130 milligrams per deciliter (mg/dL) and who have no more than one additional CVD risk factor.
- For people who already have some form of CVD or who have two or more additional risk factors for CVD, treatment combines lifestyle with lipid-lowering medications.
- People who have very high CVD risk and very high LDL-C values may take two or more medications to bring their LDL-C blood levels to a healthier range.

Some cardiologists advocate driving LDL-C levels even lower, to 70 mg/dL, in people who have severe risk for HEART ATTACK or STROKE, such as those who have already had such a cardiovascular crisis and have numerous risk factors for cardiovascular disease. For most people, reaching the LDL-C target means a decrease of 30 to 40 percent.

See also CARDIOVASCULAR DISEASE PREVENTION; CHOLESTEROL, DIETARY; CHOLESTEROL, ENDOGENOUS; GARLIC; HYPERLIPIDEMIA; LIFESTYLE AND CARDIOVASCULAR HEALTH; MEDICATIONS TO TREAT CARDIOVASCULAR DISEASE; TRIGLYCERIDE BLOOD LEVEL; TRIGLYCERIDES, DIETARY.

circle of Willis A looped network (anastamosis) of arteries at the base of the BRAIN. Branches of the internal carotid arteries form the front of the circle and branches of the posterior cerebral arteries form the back of the circle, with smaller arteries, collectively called the communicating arteries, branching from them. The circle of Willis is a unique vascular structure in the body that provides an extended safety net of redundancy for the brain's BLOOD supply; the closest analogous configuration is that of the CORONARY ARTERIES which supply the HEART. Even if damage occurs to one or two of the circle of Willis's anastomosed arteries, blood flow to the brain continues. The base of the skull protects this arterial network. The circle of Willis, because of its complexity, varies anatomically among individuals and is a common site for congenital vascular anomalies (malformations of the blood vessels).

For further discussion of the circle of Willis within the context of cardiovascular structure and function, please see the overview section "The Cardiovascular System."

See also ARTERIOVENOUS MALFORMATION (AVM); ARTERY.

congenital heart disease HEART conditions, including structural anomalies of the heart, that are present from birth. Some forms of congenital heart disease are mild to moderate and require minimal or one-time intervention to correct. Congenital heart malformations are among the most common BIRTH DEFECTS in the United States. Though still the leading cause of infant death due to birth defects, congenital heart malformations no longer mean certain death. Beginning in the 1950s pediatric cardiology pioneers Alfred Blalock (1899–1964), Helen Taussig (1898–1986), and Vivien Thomas (1910–1985) established many of the operations and surgical techniques that remain in use today to create functional BLOOD flow through malformed hearts. Advances in CARDIOPULMONARY BYPASS and refinements in surgical techniques have made relatively normal lives possible for more than a million children with heart defects born since 1970.

Structural deformities that affect the heart's ability to circulate oxygenated blood result in inadequate oxygen reaching the body's tissues and cause CYANOSIS, a bluish tint to the lips, nail beds, mucous membranes, and SKIN. Doctors collectively refer to these conditions as cyanotic heart disease (sometimes called blue baby syndrome). These conditions are nearly always apparent within 48 hours of birth and typically require fairly immediate intervention (usually surgery). Other forms of congenital heart disease, such as LONG QT SYNDROME (LQTS) and hypertrophic CARDIOMYOPATHY, may not manifest until late childhood or adulthood.

Heart defects may occur in isolation or in combination with GENETIC DISORDERS such as DOWN SYNDROME (trisomy 21) and MARFAN SYNDROME. Heart abnormalities often occur in association with

FORMS OF CONGENITAL HEART DISEASE

anomalous pulmonary venous return	aortic coarctation
AORTIC STENOSIS	atrial septal defect (ASD)
atrioventricular (AV) canal defect	bicuspid aortic valve
Eisenmenger's complex	hypoplastic left heart syndrome (HLHS)
LONG QT SYNDROME (LQTS)	patent ductus arteriosus (PDA)
persistent truncus arteriosus	pulmonary atresia
tetralogy of Fallot	transposition of the great arteries (TPA)
tricuspid atresia	ventricular septal defect (VSD)

abnormalities of the skeletal, urinary, and gastrointestinal systems, forming a collection that doctors refer to by the acronym VACTERL: vertebral, anorectal, cardiac, tracheoesophageal, renal, and limb. About 50 percent of infants born with one congenital anomaly among this grouping have at least one other. Researchers believe about 10 percent of congenital heart malformations result from GENE MUTATION or CHROMOSOME abnormalities.

Common forms of congenital heart disease The most common and most easily treatable congenital heart malformations are patent ductus arteriosus (PDA) and septal defects. The ductus arteriosus is an opening between the AORTA and the pulmonary ARTERY in the FETUS that allows fetal circulation to bypass the nonfunctioning LUNGS (the fetus draws oxygen from the mother's blood supply). At birth a sequence of events takes place, initiated with the pressure changes that occur with the infant's first breath, that cause the ductus arteriosus to close. In some infants, especially those born prematurely, the closure does not take place and the ductus arteriosus remains patent, or open. PDA allows oxygenated and deoxygenated blood to mix in the pulmonary artery, with the result that the blood the aorta sends to the body carries only partial oxygenation.

In a septal defect there is an abnormal opening in the septum, or wall, separating the heart's chambers. A septal defect allows blood to move directly between the involved chambers, which disturbs the flow of blood and can result in blood turbulence and pooling as well as reduced OXYGENATION. The most common presentation is atrial septal defect (ASD), in which the opening is between the right and left atria. The opening may be the result of incomplete closure of the foramen ovale, a natural opening between the atria in the fetus that normally closes within 48 hours of birth. ASD may also occur as a malformation of the atrial septum. A ventricular septal defect (VSD) is a malformation of the ventricular septum and results in an opening between the right and left ventricles. A VSD allows oxygenated and deoxygenated blood to mingle, reducing the oxygen content of the blood the left ventricle pumps out to the body.

Atrioventricular (AV) canal defect is a more extensive malformation of the septum in which the atrial septum, the ventricular septum, or the entire septum is missing. The heart becomes essentially a single large chamber with oxygenated and deoxygenated blood mixing freely. Blood going to the body carries insufficient oxygen, and blood going to the lungs is under much higher pressure than the lungs can accommodate. AV canal defect requires surgical repair within the first few months of the infant's life. Though AV canal defect can occur as an isolated malformation it most often occurs in conjunction with Down syndrome, affecting about 25 percent of Down syndrome infants.

Other common congenital heart defects include coarctation of the AORTA (narrowing and irregularities) and malformations of the heart valves such as AORTIC STENOSIS, bicuspid aortic valve, tricuspid atresia, and pulmonary atresia.

Grave malformations of the heart A number of heart malformations are rare, complex, and life-threatening. Their defects are severe and include alterations of the heart's structure that cannot sustain life. They require immediate surgery for survival and usually follow-up operations for further reconstruction. In some cases the only viable long-

term treatment is HEART TRANSPLANTATION. The most frequently occurring of these grave malformations are

- Tetralogy of Fallot, which is a complex of four structural anomalies: VSD, pulmonary artery and valve malformation, aortic displacement (the aorta arises between the ventricles rather than solely from the left ventricle), and hypertrophic left ventricle (thickening of the left ventricle's wall).
- Transposition of the great arteries (TGA), in which the aorta and the pulmonary artery are switched. The aorta arises from the right ventricle instead of the left, carrying the deoxygenated blood from the right ventricle out to the body. The pulmonary artery arises from the left ventricle instead of the right, taking oxygenated blood back to the lungs from the left ventricle.
- Hypoplastic (or hypotrophic) left heart syndrome (HLHS), in which the left ventricle or the entire left heart fails to develop, resulting in essentially a two-chamber heart. The aorta is usually small or deformed. Blood in the heart is a mix of oxygenated and deoxygenated, and the right ventricle pumps to both the lungs and the body.
- Persistent truncus arteriosus, which is a combination of VSD and deformities of the PULMONARY ARTERIES and aorta that disrupts the heart's ability to pump oxygenated blood to the body.
- Anomalous pulmonary venous return, in which the PULMONARY VEINS attach to the right atrium instead of the left atrium, returning oxygenated blood to the same chamber that pumps deoxygenated blood to the lungs. This malformation typically occurs in combination with ASD, so the flow of blood between the atria moves some oxygenated blood into the left atrium and subsequently the left ventricle.

Often, ULTRASOUND during PREGNANCY reveals these significant heart deformities, allowing the neonatal team to be prepared for them at the infant's birth. In many situations initial treatment includes administering PROSTAGLANDINS to maintain a patent ductus arteriosus, which allows some oxygenated blood into the body's circulation.

Congenital heart disease in adults Some forms of congenital heart disease first manifest in adulthood, such as hypertrophic cardiomyopathy and LQTS. Other forms of heart disease in adults may have congenital origins, such as the ARRHYTHMIA disorder WOLFF-PARKINSON-WHITE SYNDROME and some VALVULAR HEART DISEASE. Cardiologists believe that most situations of SUDDEN CARDIAC DEATH reflect undetected congenital heart anomalies, either structural or functional (arrhythmias). With congenital heart disease, whether undetected or previously treated, comes increased risk for ENDOCARDITIS (especially with valve malformations), arrhythmias, and clot formation leading to HEART ATTACK, STROKE, or PULMONARY EMBOLISM.

A growing number of adults had corrective surgery for congenital heart disease as infants or children. Cardiologists do not yet know the long-term effects of these operations or what precautions are necessary to protect cardiovascular health later in life. The generation born in the 1970s was the first to have these options available. As this generation comes into middle age, cardiologists will learn much about how repaired hearts accommodate the routine cardiovascular stresses of life and whether they are more susceptible to acquired forms of heart disease such as CORONARY ARTERY DISEASE (CAD) and HEART FAILURE. At present, the longest survival of infant heart transplantation is 15 years and of adolescent heart transplantation is 16 years. Rejection of the donor heart remains a significant concern, and most cardiologists expect retransplantation will become necessary for most people who receive heart transplants in infancy or childhood.

Symptoms and Diagnostic Path

The most common symptoms of congenital heart disease, notably malformations of the heart, in newborns is cyanosis and difficulty BREATHING. Congenital heart disease not immediately apparent at birth may manifest later in childhood with symptoms such as fainting with physical exertion, shortness of breath with mild activity, slowed growth, rapid heartbeat and respirations, and frequent upper respiratory infections. Young children experiencing shortness of breath often squat, which makes it easier for them to breathe.

Congenital heart disease that manifests in adulthood, such as ASD and hypertrophic cardiomyopathy, often produces symptoms such as PALPITATIONS, shortness of breath, and pulmonary or generalized EDEMA if the heart's pumping capability becomes ineffective (heart failure). The diagnostic path may include ELECTROCARDIOGRAM (ECG), ECHOCARDIOGRAM, and COMPUTED TOMOGRAPHY (CT) SCAN or MAGNETIC RESONANCE IMAGING (MRI), and CARDIAC CATHETERIZATION.

Treatment Options and Outlook

Minor congenital heart defects may require only watchful waiting. Most ASDs close within 2 years of birth and VSDs by age 7. Septal defects that persist and cause symptoms may require surgery, often via cardiac catheterization to patch the defect. Surgery is the most viable treatment option for most serious malformations of the heart. Surgery may be corrective, in which the OPERATION returns the heart to normal structure and function, or palliative, in which the operation relieves symptoms though does not restore normal structure and function. Surgery may be isolated, in which a single operation corrects the defect, or staged, in which the surgeon performs several sequential operations over a period of time. Some congenital heart malformations require surgery within days of birth, and others within months to 2 or 3 years.

When doctors detect significant congenital defects before or shortly after birth, they often administer prostaglandins to maintain a patent ductus arteriosus. Though in ordinary circumstances a PDA would be a heart defect, in the presence of congenital heart defects PDA allows continued though limited circulation of oxygenated blood to buy time until the infant is stable enough for surgery. In some circumstances the neonatal cardiologist may perform a balloon septostomy to surgically create an ASD, which further allows a mixture of oxygenated and deoxygenated blood to flow from the heart to the body.

Risk Factors and Preventive Measures

Genetic factors are emerging as the likely causes, or at least precipitating circumstances, for many forms of congenital heart disease. There are clear genetic links for conditions such as hypertrophic cardiomyopathy and LQTS, for example, as well as known correlations between specific heart malformations and genetic disorders such as Down syndrome and TURNER'S SYNDROME. As well, the VACTERL constellation of birth defects speaks to genetic underpinnings. Prevention for these kinds of heart problems remains uncertain, though future treatment is likely to include GENE THERAPY.

Some congenital heart malformations occur as the result of maternal infections such as RUBELLA (German MEASLES). Heart defects in infants are more likely to occur with mothers who have DIABETES. Numerous medications, both prescription and over-the-counter, as well as ALCOHOL consumption also cause specific kinds of birth defects. Women who are pregnant or planning to become pregnant should discuss with their doctors any routine medications they take. Many ANTISEIZURE MEDICATIONS and ANTIPSYCHOTIC MEDICATIONS are especially damaging to the developing fetus.

Despite advances in gene technology and knowledge of the body, much congenital heart disease is idiopathic—that is, doctors do not know why it occurs. Studies suggest that folic acid supplementation, which doctors already recommend to reduce the risk for NEURAL TUBE DEFECTS, also reduces the risk for malformations of the heart. Like the neurologic system, the cardiovascular system evolves early in fetal development so most malformations occur in the first weeks of pregnancy. Doctors can detect many heart abnormalities before birth, allowing parents and doctors to make appropriate treatment decisions.

See also CARDIOVASCULAR DISEASE PREVENTION; INFECTION; KAWASAKI DISEASE; SURGERY BENEFIT AND RISK ASSESSMENT; VEIN.

coronary arteries The network of arteries that encircles the HEART to provide its BLOOD supply. The two primary coronary arteries, the right coronary ARTERY and the left coronary artery, branch from the AORTA as it arises from the left ventricle. The left coronary artery is significantly larger and supplies the left heart. It drops along the left atrium, branching at the base of the left ventricle into the left anterior descending (LAD) and circumflex arteries. The circumflex artery wraps behind the heart, further branching into smaller

arteries that trail across the left ventricle. The right coronary artery traverses the right atrium, nourishing the upper right heart. Numerous smaller arteries branch from it, the largest of which is the right marginal artery. The arterial network intertwines across the front of the heart in a network called Vieussens's ring, which is similar in structure and purpose to the CIRCLE OF WILLIS at the base of the BRAIN. The precise pattern of the coronary arteries is unique for each person, however.

The coronary arteries deliver the largest volume of blood to the heart during diastole, the trough phase of the CARDIAC CYCLE during which the ventricles fill with blood, pulling blood from the aortic root as systole draws to a close. About 60 percent of the ventricular ejection goes to the coronary arteries. During systole, the peak of the cardiac cycle during which the ventricles pump blood out, the dynamic forces of the heart's contraction cause the coronary arteries to constrict.

The extensive branching of the coronary arteries provides a fairly substantial level of redundancy for supplying the heart with blood. Even if damage or occlusion blocks one branch or several branches, other arterial branches can deliver blood to the same or nearby areas to cover the deficit. As well, the heart tends to develop collateral circulation in response to arterial damage, a self-repair feature in which new small arteries sprout to extend around the area of damage. These mechanisms can sustain adequate myocardial perfusion (distribution of blood throughout the heart MUSCLE) for a considerable time, even in the face of significant damage to the heart's circulatory structures. As occlusion of the coronary arteries progresses, the collateral circulation of Vieussens's ring extends.

The efficiency of coronary circulation is such that symptoms of oxygen deficiency (notably ANGINA PECTORIS and shortness of breath with exertion) do not become apparent until damage to the coronary arteries drops blood flow to about 30 percent of normal. At this point a cardiologist may recommend ANGIOPLASTY with STENT placement. The standard diagnostic point for the more invasive CORONARY ARTERY BYPASS GRAFT (CABG) is 90 percent or greater occlusion. The symptoms of restricted blood flow become most apparent when occlusion affects the larger branches of the coronary arteries, notably the LAD and circumflex. The primary conditions that affect the coronary arteries are ATHEROSCLEROSIS, called CORONARY ARTERY DISEASE (CAD) when it involves the coronary arteries, and coronary artery spasm, which often results from CAD though may have other causes.

For further discussion of the coronary arteries within the context of cardiovascular structure and function, please see the overview section "The Cardiovascular System."

See also COCAINE; HEART ATTACK; LIFESTYLE AND CARDIOVASCULAR HEALTH.

coronary artery bypass graft (CABG) A surgical OPERATION to replace diseased CORONARY ARTERIES supplying the HEART with BLOOD. Cardiovascular surgeons began performing CABG to treat severe CORONARY ARTERY DISEASE (CAD), typically following HEART ATTACK, in the 1960s. The operation became feasible with refinements in CARDIOPULMONARY BYPASS technology and surgical technique. In the ensuing decades CABG has become one of the most frequently performed operations in the United States, with surgeons performing more than 300,000 a year. The surgeon may use CABG to replace one to five coronary arteries; three or four is most common (triple or quadruple bypass). The most frequently bypassed coronary arteries are the left anterior descending (LAD), which traverses the front of the heart; the circumflex, which wraps around the heart; and their respective branches.

Weighing the Benefits and Risks

Whether CABG is an appropriate treatment choice depends on numerous variables that include the person's age and general health status, degree and extent of occlusion in the coronary arteries, and the presence of other CARDIOVASCULAR DISEASE (CVD). Variables that strongly influence the procedure's success include lifestyle factors such as cigarette smoking, body fat and weight, physical inactivity, and dietary habits. Other health conditions that affect HEALING, such as DIABETES, are also important considerations, as are conditions affecting the LUNGS such as CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD).

Now that several million Americans have had CABG and researchers have accumulated data

spanning four decades, evidence is emerging that calls into question the ultimate effectiveness of CABG in preventing deaths due to CAD. A number of studies indicate that CABG may not extend LIFE EXPECTANCY or improve QUALITY OF LIFE to the degree cardiologists and others believe it does. Researchers continue to explore all dimensions of this debate.

Surgical Procedure

The typical CABG takes 75 to 90 minutes for the surgeon to perform. The first steps in CABG are to open the chest, initiate cardiopulmonary bypass, and stop the heart. The preferred approach for the grafts is to use the person's own blood vessels to reconstruct the occluded coronary arteries. The most viable vessels for this purpose are the right and left internal mammary arteries, which the surgeon exposes when opening the chest to perform the CABG. These arteries are ideal because they do not require additional incisions to obtain, and there is a good supply of arterial circulation to replace them. As well, the mammary arteries are about the same size as the coronary arteries, allowing them to accommodate the demands the coronary circulation will place on them. The surgeon may be able to craft two and sometimes three grafts using both internal mammary arteries. Because of its size and importance to coronary circulation, the LAD is first in line for an arterial graft. The surgeon needs about 6 inches of graft for each coronary ARTERY bypass created.

When the CABG involves more coronary arteries than the mammary arteries can accommodate, the surgeon typically harvests a segment of the saphenous VEIN from the leg, which requires an incision in the groin. Though effective enough, the saphenous vein graft is less than ideal for service as a coronary artery and is more prone to postoperative complications. Although its size makes it a sturdy vessel, the saphenous vein lacks the muscular construction of an artery and has a greater risk of collapsing or closing than does an arterial graft. As well, some people have residual edema and other complications after surgery in the leg from which the surgeon harvests the vein. An alternative practice is to instead harvest segments of arteries from elsewhere in the body for which there is relatively redundant circulation (other arteries to provide blood supply), such as the radial artery or the brachial artery in the arm. When autografts such as these are not possible, the surgeon may use a synthetic material specially treated to resist clotting. However, synthetic grafts are not as reliable as autografts.

The surgeon sutures (sews) one end of the graft into the AORTA above the occlusion and the other end into the coronary artery below the occlusion to establish the bypassed path of circulation. The surgeon does this for each occluded coronary artery. When the internal mammary artery provides the graft, the surgeon needs only to suture at the distal end because the proximal end is already in place. The diseased coronary artery segments stay in place though will no longer carry blood. When finished bypassing the occluded coronary arteries, the surgeon restores blood circulation through the heart and restarts the heart with a chemical solution or an electrical charge. After making sure the grafts are intact and not leaking, the surgeon closes the chest. Wires hold the ribs and sternum in place, while sutures and staples close the layers of MUSCLE and SKIN.

Risks and Complications

CABG entails numerous risks and complications. Though its frequency gives the perception that it is a routine operation, CABG is a significant major surgery during which the surgeon places the person on cardiopulmonary bypass, cuts through the breastbone and several ribs to expose the heart, stops the heart to reconstruct the coronary arteries, and then restarts the heart and closes the chest. Each step carries its own risks. Collectively, the major risks of CABG include

- air emboli (air bubbles that get into the bloodstream and create blockages), causing heart attack, STROKE, or PULMONARY EMBOLISM
- excessive bleeding during surgery
- bleeding when the surgeon restores circulation through the heart
- inability to restart the heart
- inability to wean from the cardiopulmonary bypass machine when surgery is done
- postbypass neurologic damage with residual consequences that may include cognitive dys-

function, memory impairment, and physical dysfunctions such as localized loss of feeling or function
- rapid restenosis (within six months) of the grafts
- collapse of venous grafts

Improved technology is making other treatment options, notably ANGIOPLASTY, increasingly viable. Some studies suggest that angioplasty with STENT placement, which is significantly less invasive and less expensive than CABG, is equally effective for multiple vessel CAD and in a good number of people lasts as long as CABG. On the other side of the debate, clinical results with all-arterial grafts for CABG show increased reliability. As well, advances in microsurgery and endoscopic surgery are making MINIMALLY INVASIVE CARDIOVASCULAR SURGERY increasingly feasible, allowing surgeons to perform minimally invasive direct coronary artery bypass (MIDCAB) procedures using multiple small incisions rather than fully opening the chest. Some surgeons are using "off-pump" procedures, in which the heart continues to function during the operation, to reduce the risk for neurologic and pulmonary side effects. Others are combining angioplasty with MIDCAB in a procedure called hybrid CABG. Researchers and surgeons continue to study these approaches and methods, comparing outcomes to determine the most appropriate options.

Outlook and Lifestyle Modifications

Most people spend three to five days in the hospital and another four to eight weeks recovering at home before making a full return to regular activities. The improvement in cardiovascular function is apparent immediately for most people. Cardiologists typically recommend cardiac rehabilitation for people who have had CABG, to help establish a structure for any necessary lifestyle modifications. The clinical standard for postoperative care now includes medications such as beta blockers and statins, drugs to stabilize HEART RATE and lower cholesterol blood levels, respectively. Statins also appear to have a stabilizing and strengthening action on the heart, with numerous clinical studies showing that people who take statins following CABG have significantly fewer complications, notably heart attack, after surgery. Cardiologists also urge people to eat nutritiously, get a minimum of 30 minutes of physical exercise each day, stop smoking, and lose weight to achieve a healthy BODY MASS INDEX (BMI). Most people experience complete and uneventful recovery from surgery and return to work and the recreational activities that interest them.

See also CARDIOVASCULAR DISEASE PREVENTION; COGNITIVE FUNCTION AND DYSFUNCTION; POSTOPERATIVE PROCEDURES; PREOPERATIVE PROCEDURES; SMOKING CESSATION; SURGERY BENEFIT AND RISK ASSESSMENT.

coronary artery disease (CAD) ATHEROSCLEROSIS of the CORONARY ARTERIES that reduces BLOOD flow to the HEART. About 14 million Americans have CAD, though many of them do not know it until HEART ATTACK strikes. CAD causes 1.2 million heart attacks and more than 600,000 deaths in the United States every year. Autopsy findings show that two thirds of women and nearly half of men who lose their lives to SUDDEN CARDIAC DEATH had unsuspected CAD. Although CAD is more common in people age 60 and older, it is becoming increasingly common among younger people. Genetic factors may underlie CAD in some people, though most often CAD is an acquired condition that is the direct consequence of lifestyle factors such as cigarette smoking, EATING HABITS, and physical inactivity.

HEART ATTACK is a life-threatening emergency. Call 911 immediately with symptoms or when heart attack is possible. Many people delay, wanting to be sure. Waiting can be fatal.

CAD, like generalized atherosclerosis, develops over decades. Many cardiologists believe CAD begins in childhood. The most commonly affected coronary arteries are the left anterior descending (LAD), the circumflex, and their branches. These coronary arteries provide the blood supply for most of the heart MUSCLE, including nearly all of the left ventricle. CAD may affect the right coronary ARTERY as well. Cardiologists classify CAD according to the number of occluded coronary arteries. A coronary artery can be 70 percent occluded before the restricted blood flow impairs

cardiac function, though cardiologists believe reduced OXYGENATION begins with about 50 percent occlusion. The heart's ability to develop collateral circulation, the growth of new arteries, allows CAD to worsen without overtly affecting cardiac function.

CAD develops when ATHEROSCLEROTIC PLAQUE infiltrates the arterial intima, the innermost layer of the arterial wall, and accumulates into deposits called atheromas. The atheromas cause the arterial wall to thicken, reducing its elasticity and thus its ability to contract and expand in response to blood flow needs. Atheromas also protrude into the channel of the artery, reducing the artery's interior diameter (lumen) and reducing the volume of blood the artery can transport. These factors converge to restrict blood flow to the heart, particularly with exertion (such as during physical exercise), and deprive segments of the heart of adequate oxygenation. The result is ischemia, or tissue HYPOXIA. Typically the ischemia eases with rest, as the heart's demand for oxygen diminishes.

Symptoms and Diagnostic Path

The key symptom of CAD is ANGINA PECTORIS, a pressurelike discomfort or pain originating in the central chest and often radiating up the arm into the jaw and through the shoulder area to the back. At this stage, medical or surgical interventions can head off CAD-induced heart attack. For many people, however, the first indication of CAD is heart attack, which can occur when an atherosclerotic coronary artery ruptures or a blood clot lodges in a section of a coronary artery where CAD has narrowed the passageway. The resulting blockage, or occlusion, interrupts blood flow to a portion of the heart and the heart tissue dies.

CARDIAC CATHETERIZATION and ANGIOGRAM provide definitive diagnosis. These procedures allow the cardiologist to visualize the path of blood through the coronary arteries, highlighting constricted or blocked areas. Severe CAD also causes ARRHYTHMIA (disturbance of the heart's electrical activity), which a person may experience as PALPITATIONS and that show up on ELECTROCARDIOGRAM (ECG). Exercise STRESS TEST, particularly radionuclide testing, reveals the functional limitations resulting from the CAD. ECHOCARDIOGRAM often reveals the dysfunction of the walls of the heart served by diseased coronary arteries, as well as decreased heart function if there has already been damage, and with Doppler ULTRASOUND may show restrictions in the flow of blood.

Some cardiologists use MAGNETIC RESONANCE IMAGING (MRI) to visualize the structure and function of the coronary arteries and the rest of the heart. MRI also detects new collateral circulation (angiogenesis). However, anyone who has a PACEMAKER, IMPLANTABLE CARDIOVERTER DEFIBRILLATOR (ICD), stents, ANEURYSM clips, or other internal metallic objects cannot undergo MRI. An advantage of MRI is its ability to represent dimensional cross-sections of the areas of suspected atherosclerotic accumulation. This reveals the extent to which the CAD has caused the arterial wall to thicken.

A variation of CT scan, ELECTRON BEAM COMPUTED TOMOGRAPHY (EBCT) SCAN, can detect calcification in the arterial walls. Calcification indicates long-standing accumulations of plaque that have solidified within the intima, a sign of well-established CAD that, while perhaps not causing symptoms, is significant enough to pose the risk of heart attack. Of equal, and perhaps greater, concern to cardiologists is the accumulation of soft, unstable atherosclerotic plaque, sometimes called vulnerable atheroma. These soft accumulations appear to cause continued irritation to the arterial wall, with resulting clot formation and the risk that the atherosclerotic plaques will rupture, spilling particles and debris into the blood circulation.

Treatment Options and Outlook

Although CORONARY ARTERY BYPASS GRAFT (CABG) remains the leading treatment for CAD in the United States, cardiologists are moving toward less invasive approaches. CABG is an OPEN HEART SURGERY with numerous risks and complications. A number of studies in the late 1990s and early 2000s raised questions as to whether CABG provides a clear benefit over other treatment alternatives such as ANGIOPLASTY, aggressive lipid-lowering therapy, and significant lifestyle modifications. Cardiologists now implement the latter two methods after CABG, and there is increasing evidence that they are equally effective without CABG. Angioplasty, a cardiac catheterization procedure in which a balloon at the tip of a catheter compresses

the occlusion, remains a popular intervention because it is far less invasive than CABG, requires minimal recovery time, and results in immediate improvement of coronary circulation. However, restenosis (return of the atherosclerotic narrowing) is more the norm than the exception and occurs in a fourth to a third of people within six months. Angioplasty with STENT placement (a tiny springlike device that remains at the site of the occlusion to hold pressure against the arterial wall) fares somewhat better. Treatment options and recommendations continue to evolve as new medications and technologies become available.

The most significant long-term consequence of CAD is damage following heart attack, which may or may not improve with CABG. LEFT VENTRICULAR EJECTION FRACTION (LVEF), a calculation of the percent of blood that leaves the heart with each contraction of the left ventricle, projects the extent of disability resulting from heart attack due to CAD. LVEF above 60 percent generally correlates with little loss of cardiovascular function except with extreme physical exertion. Most people with an LVEF greater than 40 percent can return to work and normal activities. LVEF that drops below 40 percent limits the heart's capacity to meet the body's oxygen needs during moderate physical exertion, and below 20 percent restricts nearly all physical activity.

MAJOR RISK FACTORS FOR CAD

age 50 or older	cigarette smoking
DIABETES	family history of young HEART ATTACK
HYPERLIPIDEMIA	HYPERTENSION
OBESITY	PERIPHERAL VASCULAR DISEASE (PVD)
physical inactivity	

Risk Factors and Preventive Measures

The most clear-cut early warning sign for the development of CAD is HYPERLIPIDEMIA (elevated cholesterol and triglycerides blood levels). Hyperlipidemia indicates dysfunction with the body's lipid synthesis and storage mechanisms, which typically results in accumulations of fatty acids along the inner arterial walls. These accumulations irritate and inflame the artery's intima, establishing the foundation for atherosclerotic plaque development. Numerous studies show that lowering blood lipid levels reduces atherosclerotic accumulations, slowing the progression of CAD. DIABETES, HYPERTENSION, and OBESITY accelerate the progression of CAD. The prevalence of CAD in young people alarms health experts, who emphasize that it is never too early to implement a heart-healthy lifestyle.

An important understanding about CAD is that it is a chronic, lifelong cardiovascular condition. Even with CABG or angioplasty, the disease process continues. Treatments aim to slow the progression but so far are not able to prevent it. Lifestyle changes are imperative for people who want to enjoy extended LIFE EXPECTANCY as well as QUALITY OF LIFE. Though the outlook for controlling CAD has never been brighter, CAD remains a major health concern. Lifestyle modifications to improve cardiovascular health, in combination with medical interventions such as ASPIRIN THERAPY and medications to regulate heart function, can significantly impede CAD's progression.

See also CARDIOVASCULAR DISEASE PREVENTION; COENZYME Q10; DIABETES AND CARDIOVASCULAR DISEASE; DIET AND CARDIOVASCULAR HEALTH; PHYSICAL EXERCISE AND CARDIOVASCULAR HEALTH; SMOKING AND CARDIOVASCULAR DISEASE; STROKE.

c-reactive protein A substance the body's tissues release when they become inflamed. Some health experts believe elevated levels of c-reactive protein in the BLOOD may indicate the presence of ATHEROSCLEROSIS. Though cardiologists and researchers have known for some time that inflammatory processes accompany atherosclerosis, studies in the 1990s and early 2000s began to suggest that INFLAMMATION, perhaps due to low-grade INFECTION, might be a contributing cause of atherosclerosis. Elevated blood levels of c-reactive protein in people who have had HEART ATTACKS portend significant increase in risk for subsequent HEART attacks. However, cardiologists are not certain how important elevated c-reactive protein levels are in people who do not appear to have CARDIOVASCULAR DISEASE (CVD). Chronic inflammatory conditions may also elevate c-reactive protein. Cardiologists generally recommend considering a person's level of c-reactive protein in context with other RISK FACTORS FOR CARDIOVASCULAR DISEASE, and base intervention decisions on the overall cardiovascular risk picture.

See also COENZYME Q10; HEART ATTACK; LIFESTYLE AND CARDIOVASCULAR HEALTH; VITAMINS AND HEALTH.

cyanosis A bluish coloration to the lips, nail beds, and SKIN that indicates inadequate oxygenation. Clinically, cyanosis exists when the oxygen saturation of arterial BLOOD drops below 85 percent. Cyanosis may result from conditions that affect the ability of the LUNGS to oxygenate the blood, such as may occur with CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD), or that affect cardiac function, such as HEART FAILURE or MYOCARDIAL INFARCTION (HEART ATTACK). Cyanosis may also result from severe ANEMIA and other blood disorders that affect the blood's ability to transport oxygen. Poisoning with mercury or silver can cause the skin to take on a bluish hue, as can certain antipsychotic medications. Doctors call this pseudocyanosis because it is not the result of the blood's oxygen levels.

See also CONGENITAL HEART DISEASE; HEAVY METAL POISONING; HYPOXIA; RAYNAUD'S SYNDROME.

D

DASH eating plan The acronym for "dietary approaches to stop HYPERTENSION." The DASH eating plan is the result of a pair of clinical research studies and features a diet high in fruits, vegetables, low-fat dairy products, whole grain products, and low in fats (particularly saturated fats) and sodium. Numerous studies correlate dietary habits, particularly sodium consumption, with hypertension. The DASH eating plan is appropriate for anyone to follow to maintain cardiovascular health. The plan, available through health-care providers and online from the National Heart, Lung, and Blood Institute (NHLBI) at www.nhlbi.nih.gov, features menus and extensive food choices to help people plan nutritious meals that help lower BLOOD PRESSURE. It also provides guidelines for transitioning to more heart-healthy eating and other lifestyle habits.

See also CARDIOVASCULAR DISEASE PREVENTION; DIET AND CARDIOVASCULAR HEALTH; EATING HABITS; PHYSICAL EXERCISE AND CARDIOVASCULAR HEALTH.

defibrillation A therapeutic method for delivering an electrical shock to the HEART to restore it to a functional rhythm. Defibrillation is an emergency treatment necessary to prevent death resulting from VENTRICULAR FIBRILLATION (rapid, discordant, and ineffective contractions that fail to pump BLOOD out of the heart). The body cannot survive in ventricular fibrillation for longer than a few minutes, making rapid response essential. The most common causes of ventricular fibrillation are MYOCARDIAL INFARCTION, arrhythmic cardiac disease such as LONG QT SYNDROME (LQTS), ELECTROCUTION, and drowning.

In hospital-based defibrillation, a health-care professional (usually a doctor) places paddles or electrodes on the outside of the chest. The defibrillator machine delivers the determined electrical impulse, generally producing a pronounced jolt in the person's body. The desired effect is for all electrical activity in the heart to momentarily cease, then for the heart to resume normal electrical activity to the extent possible in the context of damage that may have occurred to the heart. The doctor may choose to administer multiple charges, depending on the response and the likelihood for successful restoration of a regular HEART RATE.

In the 1990s a basic portable device, the AUTOMATED EXTERNAL DEFIBRILLATOR (AED) became available. AEDs allow virtually anyone to administer a potentially lifesaving electrical shock to someone who is experiencing ventricular fibrillation. The computerized programming of an AED reads the ELECTROCARDIOGRAM (ECG) of the person to confirm the ventricular fibrillation, then delivers a preset electrical shock. AEDs have saved countless lives.

The risks of defibrillation include electrical BURNS to the person being resuscitated and electrical shock or burns to the person administering defibrillation. Burns may occur at the contact points of the paddles or electrodes and also elsewhere on the body where there are items of metal such as jewelry or, in a hospital setting, monitoring electrodes. As well, anyone in contact with the person or with the bed the person is lying on is at risk for contact electrical shock. The success of defibrillation depends on the cause of the ventricular fibrillation, how long the heart has been in ventricular fibrillation, and the person's overall cardiovascular and general health status.

See also ARRHYTHMIA; CARDIOPULMONARY RESUSCITATION (CPR); CARDIOVERSION.

deep vein thrombosis (DVT) The formation of BLOOD clots in the veins, usually the deep or inte-

rior veins in the legs and lower pelvis. Physical inactivity is the primary cause of DVT. The veins, which are not as muscular as the arteries, rely on the skeletal MUSCLES to support them. The contraction and relaxation of skeletal muscles, such as occurs during walking and other physical activities, helps move blood through the veins. This support and massaging action is particularly important for function of the large veins in the legs, which transport significant volumes of blood toward the HEART against pressure that can reach three times the force of gravity.

During periods of extended inactivity the skeletal muscles relax the tension they otherwise would exert against the veins, allowing the flow of blood to become sluggish. When other problems with the veins exist, such as VENOUS INSUFFICIENCY (inadequate function of the valves in the veins) and VARICOSE VEINS, blood may pool. The pooling provides opportunity for the blood to begin clotting, which can cause the localized occlusion and PAIN that characterizes DVT as well as HEART ATTACK, STROKE or PULMONARY EMBOLISM (blood clot in the LUNG) if a particle of the clot breaks away and travels through the bloodstream.

Birth control pills, even low-DOSE formulations, increase the risk for deep vein thrombosis, most significantly in women who also smoke.

The most effective approach for DVT is prevention, which for many people can be as simple as walking for a few minutes every couple hours during the day, even if only around a desk or lifting the legs as if marching in place. Additional risk factors include OBESITY, DIABETES, VARICOSE VEINS, PERIPHERAL VASCULAR DISEASE (PVD), and cigarette smoking. Doctors may recommend ANTICOAGULATION THERAPY as a further preventive measure to reduce the blood's clotting ability for people who are at risk for developing DVT. Though extended airline flights present a well-popularized risk for DVT, less than one tenth of 1 percent of the 2 million Americans who develop DVT do so as a result of flying.

Once the thrombosis, or clot, develops it blocks the flow of blood, which results in a backup of fluid that seeps into the surrounding tissues (edema). The clot also irritates the walls of the VEIN, causing INFLAMMATION. Symptoms of DVT include

- redness and swelling (edema) at the site of the clot
- tenderness or PAIN at the site of the clot
- FEVER and generalized discomfort

The diagnostic path may include ULTRASOUND or VENOGRAM of the suspected occlusion, which typically provides the visualization necessary to confirm the diagnosis. Treatment typically consists of

- anticoagulation therapy to prevent the clot from enlarging or other clots from forming
- bed rest, with heat to the area to improve circulation, until the clot dissolves
- support stockings

People who have one experience with DVT face increased risk for subsequent DVTs and usually take prophylactic anticoagulation therapy to lower the risk. Lifestyle measures such as daily walking and other physical activity, SMOKING CESSATION, and weight loss if necessary are also key to preventing subsequent DVTs.

See also CARDIOVASCULAR DISEASE PREVENTION; COAGULATION; LIFESTYLE AND CARDIOVASCULAR HEALTH; WALKING FOR FITNESS; WEIGHT LOSS AND WEIGHT MANAGEMENT.

diabetes and cardiovascular disease A leading consequence of DIABETES (type 1 or type 2) is CARDIOVASCULAR DISEASE (CVD), and diabetes is a leading cause of cardiovascular disease. The extent to which diabetes and cardiovascular disease intertwine has caused some health experts to view diabetes as a form of cardiovascular disease. Among people with diagnosed diabetes, more than 95 percent have some form of cardiovascular disease, the most common being HYPERLIPIDEMIA (elevated BLOOD levels of cholesterol and triglycerides) and HYPERTENSION (high BLOOD PRESSURE).

Diabetes causes numerous changes in the body that influence or accelerate the development of cardiovascular disease. Key among them are

- dysfunctions of lipid METABOLISM that result in elevated blood levels of low-density lipoprotein

cholesterol (LDL-C) and very low density lipoprotein cholesterol (VLDL-C), and lowered blood levels of high-density lipoprotein cholesterol (HDL-C)

- altered myocardial cell structure and activity, resulting in CARDIOMYOPATHY (myocardial dysfunction)
- increased levels of fibrinogen and clotting substances that increase the blood's tendency to clot, raising the risk for STROKE and HEART ATTACK
- elevated blood GLUCOSE levels damage peripheral blood vessels and the nerves that supply them, raising the risk for PERIPHERAL VASCULAR DISEASE (PVD)
- damage to the glomerular structures of the KIDNEYS, resulting in NEPHROPATHY of diabetes and its slate of complications, key among them being hypertension

Cigarette smoking, itself a significant risk factor for cardiovascular disease, doubles the cardiovascular risk of diabetes in people who smoke and have diabetes. Increasing age is a risk factor for both diabetes and cardiovascular disease. As well, diabetes slows HEALING, increasing the risk for complications with surgical treatment options for forms of cardiovascular disease such as CORONARY ARTERY DISEASE (CAD).

Early diagnosis of INSULIN RESISTANCE with lifestyle and medication, if appropriate, to delay its progression to type 2 diabetes, improves the cardiovascular risk. Once diabetes develops, meticulous control of blood glucose levels slows many of the changes that create increased risk for cardiovascular disease. Aggressive medical interventions such as lipid-lowering medications, ASPIRIN THERAPY, and antihypertensive measures (lifestyle, medication, or both) help moderate risks related to changes in lipid, clotting, and blood pressure mechanisms.

Health experts recommend these targets for people who have diabetes to lower their risk for cardiovascular disease:

- A1c (also called HbA1c or glycohemoglobin)—6 percent or lower (indicates blood glucose levels over time)
- blood pressure—129/79 millimeters of mercury (mm Hg) or lower
- LDL-C —100 milligrams per deciliter (mg/dL) or lower
- BODY MASS INDEX (BMI)—24.9 or lower (healthy weight)
- no smoking
- 30 minutes of moderate physical exercise (such as walking) daily

With diligent control of diabetes and efforts to reduce cardiovascular disease risks, most people who have diabetes can achieve near-normal cardiovascular health for years to decades.

See also CARDIOVASCULAR DISEASE PREVENTION; CHOLESTEROL BLOOD LEVELS.

diet and cardiovascular health The influence of eating habits and food consumption on the health and function of the cardiovascular system. Researchers first conclusively connected diet with cardiovascular health in the 1950s when they recognized that dietary fat was a key source of cholesterol for the body. Health experts issued the first statements about this correlation in the early 1960s. Though researchers now understand much more about how the body acquires and uses NUTRIENTS, they continue to investigate the ways in which dietary factors, independent of as well as in conjunction with other lifestyle variables such as physical exercise, affect cardiovascular health. Much of this research has focused on the role of dietary cholesterol and fats, as excesses of these nutrients in the body are key RISK FACTORS FOR CARDIOVASCULAR DISEASE (notably ATHEROSCLEROSIS).

Through the years doctors have recommended various "diets" (proportions and restrictions of nutrients) to support cardiovascular health and reduce the risk for CARDIOVASCULAR DISEASE (CVD). Research has shown, however, that variety and moderation are factors most important for meeting the body's nutritional needs. The body needs carbohydrates, proteins, and fats—the core nutrients—in varying proportions according to age, activity level, and other variables. Rather than focusing on these proportions, however, health experts recommend instead shifting emphasis to the kinds of foods consumed to

- eat more vegetables, fruits, whole grain products, low-fat dairy products, lean meats (especially fish and poultry)
- eat fewer processed foods, which tend to be high in fats, carbohydrates, and sodium
- balance the number of calories consumed with the number of calories expended through physical exercise

Many people consume far more fats and carbohydrates than they realize, so returning to nutritionally balanced EATING HABITS may at first seem restrictive in the context of a "diet." Portion size is a significant factor as well. The intent of HEART-healthy eating is to supply the body with the nutrients it needs through food choices that appeal to the individual.

The body also needs a wide range of vitamins and minerals to carry out its functions and processes. Minerals such as calcium, potassium, sodium, and magnesium are additionally important for cardiovascular function. These minerals, called electrolytes because they conduct electrical current, facilitate and regulate the electrical activity in the HEART that causes it to contract. The KIDNEYS also use electrolytes to adjust the body's fluid balance, a key aspect of BLOOD PRESSURE regulation. Excessive electrolyte consumption (such as sodium, the primary ingredient of table salt) or insufficient electrolyte consumption (such as results with prolonged VOMITING and DIARRHEA) alters the body's fluid balances, which affects blood pressure and cardiac workload.

In recent years much attention has focused on nutrients that appear to inhibit or even prevent disease processes. Key among them in regard to cardiovascular health are ANTIOXIDANTS, omega fatty acids, and SOY. Antioxidants are chemicals that counter the effects of oxidation, a normal dimension of METABOLISM, in the body. Oxidation represents "spent" fuel, the remnants of energy generation. Oxidation produces molecular fragments called free radicals that randomly attach themselves to other molecules. When they do so, they create molecular structures that are not useful to the body. Researchers believe the accumulation of free radicals is a dominant factor in health conditions such as atherosclerosis and CORONARY ARTERY DISEASE (CAD). Antioxidants bind with free radicals, creating molecular structures the body can eliminate as cellular waste. Vitamins A, C, and E contain antioxidants that may slow the progress of atherosclerosis. Another ANTIOXIDANT, COENZYME Q10, also appears to have a measurable effect in slowing atherosclerotic processes.

Omega fatty acids are polyunsaturated fats—the "good" fats—that help to lower low-density lipoprotein cholesterol (LDL-C) and also help to prevent ATHEROSCLEROTIC PLAQUE from accumulating. Sources of omega fatty acids are cold-water fish such as tuna, salmon, mackerel, lake trout, herring, and sardines. Soybeans and soy-based foods such as tofu contain alpha linolenic acid (ALA), which is an omega fatty acid precursor (the body can convert it to omega fatty acid).

See also CALORIE; CARDIOVASCULAR DISEASE PREVENTION; MINERALS AND HEALTH; NUTRITIONAL ASSESSMENT; OMEGA FATTY ACIDS AND CARDIOVASCULAR HEALTH; PHYSICAL EXERCISE AND CARDIOVASCULAR HEALTH; SOY AND CARDIOVASCULAR HEALTH; VITAMINS AND HEALTH.

echocardiogram A noninvasive, diagnostic ULTRASOUND examination of the HEART that can show the heart's structure and, when combined with Doppler technology, the flow of BLOOD through the heart's chambers and the CORONARY ARTERIES. Echocardiogram is most effective for evaluating VALVULAR HEART DISEASE and structural malformations of the heart such as major congenital deformities, septal defects, and patent ductus arteriosus (PDA).

There is no preparation for a echocardiogram, which uses soundwaves to create visual images. For a transthoracic echocardiogram (TTE), the ultrasonographer places a small amount of gel on the SKIN of the chest to improve contact with the transducer, the device that sends and receives the sound signals. The ultrasonographer then moves the transducer over the surface of the skin. For a transesophageal echocardiogram (TEE), the ultrasonographer numbs the back of the THROAT and passes a narrow cable with a transducer at the tip down the throat into the ESOPHAGUS. A TEE places the transducer as close as possible to the heart, usually to obtain specific images such as to detect septal defects or certain valve malformations.

A computer converts the sound signals into two- or three-dimensional images. Typically the cardiologist does an ELECTROCARDIOGRAM (ECG) at the same time, to correlate the visual images from the echocardiogram with the heart's electrical activity. Sometimes the cardiologist will combine the echocardiogram with an injection of dye, administered intravenously, to better highlight the inner structures of the heart. Echocardiogram or TTE takes 10 to 20 minutes and there is no recovery time necessary after the procedure. People undergoing TEE generally receive sedation before the procedure begins so go to a recovery area after the TEE until fully awake from the sedative and the cardiologist is satisfied there will be no adverse effects.

CONDITIONS ECHOCARDIOGRAM CAN HELP DIAGNOSE OR MONITOR

AMYLOIDOSIS	aortic ANEURYSM
AORTIC STENOSIS	CARDIAC TAMPONADE
CARDIOMYOPATHY	congenital heart malformations
ENDOCARDITIS	HEART FAILURE
HEMACHROMATOSIS	mitral valve prolapse
MYOCARDIAL INFARCTION	MYOCARDITIS
MYXOMA	patent ductus arteriosus
PERICARDITIS	PRIMARY PULMONARY HYPERTENSION
septal defect	VALVULAR HEART DISEASE

See also ANGIOGRAM; COMPUTED TOMOGRAPHY (CT) SCAN; CONGENITAL HEART DISEASE; MAGNETIC RESONANCE IMAGING (MRI).

ectopic beat An extra or additional heartbeat. Ectopic beats can be atrial, called premature atrial contractions (PACs), or ventricular, called premature ventricular contractions (PVCs). PACs are nearly always benign (do not require treatment). Though most PVCs are also benign, persistent PVCs can cause symptoms that do require treatment. CAFFEINE is a common cause of ectopic beats. ALCOHOL use, cigarette smoking, and illicit drugs also can cause or exacerbate ectopic beats.

The most common symptom of ectopic beat is PALPITATIONS, the perception of the heart jumping or skipping a beat though it actually does neither. Ectopic beats are premature—that is, they are normal contractions that occur before their normal rhythm in the CARDIAC CYCLE. The beat that follows, also a normal beat, then feels intensified. An ELECTROCARDIOGRAM (ECG) shows the heart's electri-

cal pattern, including ectopic beats. Their place in the cardiac cycle and their frequency determine whether ectopic beats are part of an ARRHYTHMIA that is potentially harmful. When this is the case, the cardiologist will conduct further diagnostic testing to determine the underlying causes and guide treatment decisions.

Though ectopic beats are really not preventable, reducing factors that contribute to irregularities in the heartbeat, such as caffeine consumption, often help significantly reduce their occurrence.

See also ATRIAL FIBRILLATION; MEDICATIONS TO TREAT CARDIOVASCULAR DISEASE; PREMATURE VENTRICULAR CONTRACTION (PVC).

electrocardiogram (ECG) A noninvasive diagnostic procedure that converts the heart's electrical activity into patterns of signals typically recorded on paper or displayed on a screen. The ECG is the cornerstone of cardiovascular diagnosis. The normal HEART generates a consistent electrical pattern; nearly anything that goes wrong with the heart shows up on an ECG. A normal heart rhythm produces five predictable fluctuations, called waves, that doctors identify by the letters P, Q, R, S, and T. The main thrust of cardiac activity, ventricular contraction, is the QRS complex.

ECG TRACING

P wave	sinoatrial (SA) node's pacing impulse initiates the CARDIAC CYCLE
Q wave	pacing impulse arrives at the ventricular apex
R wave	main ventricular contraction
S wave	completion of ventricular contraction
T wave	heart's return to readiness for the next cardiac cycle

Reasons for Doing This Test

ECG is a common procedure to assess the function of the heart. It can be baseline, diagnostic, or monitoring. A baseline ECG is generally part of a ROUTINE MEDICAL EXAMINATION and establishes a record of the heart's activity when the heart is presumably healthy. A baseline ECG provides a standard for comparison should there be cardiovascular symptoms the cardiologist needs to evaluate. The cardiologist does a diagnostic ECG to examine the heart's electrical activity as it may correlate to symptoms the person is experiencing. The most common symptoms for which doctors conduct diagnostic ECGs are CHEST PAIN and PALPITATIONS. A monitoring ECG checks the heart's rhythm as a means of evaluating whether medications are working effectively to treat ARRHYTHMIA or to determine whether the heart's function is stable following heart surgery or a cardiac crisis such as HEART ATTACK.

Preparation, Procedure, and Recovery

It is a good idea to avoid CAFFEINE and cigarettes for an hour or so before a scheduled ECG. Doctors generally prefer for ECG to show the heart at rest and prefer people not engage in strenuous exercise within four hours of ECG. Otherwise, ECG requires no preparation and may take place in the doctor's office, at a cardiovascular testing facility, or a hospital. The person lies quietly on a gurney or procedure bed and the ECG technician places about a dozen electrodes on the chest, back, arms, and legs. Talking or moving during the ECG can produce electrical "static" from the muscles. A typical ECG takes about five minutes to complete. Though the reading is immediately available, a cardiologist must interpret it and usually it takes a day for the doctor to report the results back for a routine ECG. The person may go home after the ECG recording is finished.

Variations on the standard ECG procedure include

- Holter monitor or ambulatory ECG, which uses a small, battery-operated unit the person wears on a shoulder strap or belt to monitor the heart's electrical activity over a period of time, typically 24 hours (an ECG technician places the electrodes on the person's chest and back and connects them to the unit)
- Exercise ECG, in which the person walks at varying paces on a treadmill or rides a stationary bicycle while the ECG records the heart's changes in rhythm
- Event ECG, in which the person wears electrodes attached to a small, battery-operated unit that the person turns on during a cardiac event such as palpitations

Risks and Complications

There are no risks or complications associated with ECG. Sometimes the ECG technician must shave a small area of SKIN to allow good electrode contact. Some people who are highly sensitive to adhesive may have a slight skin reaction to the adhesive pad that holds the electrode in place. And some people quickly chill when lying on the procedure table; the ECG technician can cover the person with a warm blanket for improved comfort and to prevent shivering, which can distort the ECG reading. ECG only detects and records the electrical activity of the heart; it does not send any electrical impulses to the heart.

See also AUTOMATED EXTERNAL DEFIBRILLATOR (AED); CARDIOVERSION; DEFIBRILLATION; ECHOCARDIOGRAM.

electrophysiology study (EPS) A diagnostic procedure in which the cardiologist inserts electrodes into the HEART to measure the heart's rhythm and response to various stimuli. The EPS is similar to CARDIAC CATHETERIZATION and provides information to help diagnose disorders of ARRHYTHMIA. The EPS takes place in a hospital or cardiac catheterization laboratory setting and is a same-day procedure for most people. Preparation consists of no food or drink the night before the procedure. The person undergoing the EPS needs a family member or friend to drive to and from the hospital.

After administering a general sedative and a local anesthetic, the cardiologist threads several catheters through an incision in the groin into the femoral vein and then through the arterial network to the heart, watching their progress via FLUOROSCOPY. Once in the heart, the leads on the tips of the catheters send back electrical impulses similar to an ELECTROCARDIOGRAM (ECG). The cardiologist may administer medications or mild electrical impulses to assess the heart's response and ability to return to a normal rhythm.

An EPS takes three to four hours to complete. After the procedure is over, the person goes to a recovery area until he or she is fully awake from the sedative and the cardiologist is satisfied there will be no adverse effects. Sometimes the cardiologist will want the person to stay overnight in the hospital for cardiovascular monitoring. Most people experience mild to moderate discomfort in the groin area where the cardiologist inserted the catheters, and occasionally this is the site for post-procedure bleeding. The EPS provides comprehensive information about the heart's electrical activity.

See also ECHOCARDIOGRAM; STRESS TEST.

endarterectomy An OPERATION to surgically remove accumulations of ATHEROSCLEROTIC PLAQUE (atheromas) from the arteries. The most common site for endarterectomy is the carotid arteries, which carry BLOOD to the head and BRAIN. Endarterectomy is a major surgery done under general ANESTHESIA, typically with 24 to 48 hours of inpatient hospitalization following the OPERATION. During endarterectomy, the surgeon makes a small incision through the SKIN and into the ARTERY at the site of the atheroma, briefly stops the flow of blood through the artery and removes the atheroma, restores blood flow, and sutures the artery closed. Depending on the location and size of the atheroma the surgeon may place a shunt in the artery to allow blood to flow around the site of the atheroma during the operation. The shunt maintains blood supply to the brain and helps prevent atherosclerotic fragments from escaping into the blood flow to the brain.

Endarterectomy is a fairly high risk procedure because of the potential for dislodging fragments of the atheroma during the procedure. When this happens, there is no way to prevent the fragments from traveling up the carotid artery to the brain where they cause STROKE. About 3 percent of people who undergo endarterectomy experience stroke, ranging in severity from imperceptible symptoms to disability or death. Cardiologists recommend endarterectomy when the occlusion is 80 to 99 percent. Studies show that endarterectomy can lower the risk for stroke even when CAROTID STENOSIS does not cause symptoms, though because of the risk that the operation itself can result in stroke, some cardiologists recommend surgery only when the blockage causes symptoms.

See also CORONARY ARTERY BYPASS GRAFT (CABG); POSTOPERATIVE PROCEDURES; PREOPERATIVE PROCEDURES; SURGERY BENEFIT AND RISK ASSESSMENT.

endocarditis INFLAMMATION of the ENDOCARDIUM, the lining of the HEART. Viral or bacterial INFECTION

can cause endocarditis; either is potentially life threatening, though bacterial infection is considerably more common. Bacterial endocarditis is a particular risk for people who have certain forms of CARDIOVASCULAR DISEASE (CVD) and may follow bacterial infection in other parts of the body. Pathogenic (infection-causing) BACTERIA may also enter the BLOOD circulation during dental, diagnostic, and surgical procedures that cause bleeding. Endocarditis also occurs as a complication following valve repair or replacement surgery.

CARDIOVASCULAR CONDITIONS THAT INCREASE RISK FOR ENDOCARDITIS

cardiopulmonary shunt	cyanotic CONGENITAL HEART DISEASE
HEART TRANSPLANTATION	hypertrophic CARDIOMYOPATHY
mitral valve prolapse	previous bacterial endocarditis
prosthetic heart valves	RHEUMATIC HEART DISEASE
uncorrected congenital heart malformations	VALVULAR HEART DISEASE

Symptoms may include COUGH, shortness of breath (DYSPNEA), and CHEST PAIN. Mild to moderate FEVER, weight loss, night sweats, and JOINT pain are also common. Symptoms vary with the location and nature of the infection and are often vague, making it challenging for doctors to connect them to the heart. The diagnostic path includes blood cultures to determine the presence of bacteria and ECHOCARDIOGRAM to affirm the inflammation.

Treatment for bacterial endocarditis is intensive antibiotic therapy, administered intravenously in a hospital inpatient setting. Treatment for viral endocarditis is supportive, sometimes requiring hospitalization to administer intravenous fluids and medications to ease the heart's workload until the infection runs its course. Complications of either form include endocardial abscesses, valvular abscesses, and damage to the heart valves. With appropriate treatment most people recover, though some may have residual consequences (such as valve disease) and increased risk for subsequent infections.

See also ABSCESS; ANTIBIOTIC PROPHYLAXIS; MYOCARDITIS; PERICARDITIS; VIRUS.

endocardium The membrane that lines the inner HEART, made up of epithelial cells. The endocardium also covers the heart valves, providing a smooth surface that offers no opportunity for BLOOD cells (particularly platelets) to stick to it as they pass through the heart. The endocardium contains Purkinje fibers, specialized MUSCLE cells that convey the electrical impulses that cause the heart to contract, and collagen fibers, which give the endocardium elasticity. The endocardium is vulnerable to damage from conditions such as RHEUMATIC HEART DISEASE and VALVULAR HEART DISEASE. These conditions can cause irritation that inflames the endocardium, making it susceptible to bacterial INFECTION (ENDOCARDITIS).

For further discussion of the endocardium within the context of cardiovascular structure and function, please see the overview section "The Cardiovascular System."

See also BACTERIA; MYOCARDIUM; PERICARDIUM; PLATELET.

enhanced external counterpulsation (EECP) A therapy for ANGINA PECTORIS that uses sequential inflation and deflation of cuffs on the legs and pelvis to assist in returning venous BLOOD to the HEART and decreasing cardiovascular resistance in the peripheral arteries. EECP reduces the heart's workload during systole, when the ventricles contract, and increases pressure in the peripheral arterial network during diastole, when the ventricles fill. The net effect is that the body's tissues, including the heart, receive more blood and thus more oxygen with less work from the heart.

Researchers arrived at the concept of EECP in the 1950s. Initial therapeutic efforts were invasive, withdrawing blood from the femoral veins and then returning it. Through the ensuing decades researchers arrived at the method of using compression cuffs around the calves, thighs, and pelvis, alternately inflating and deflating them in a sequence timed with the CARDIAC CYCLE. The cuffs inflate sequentially from the calves to the pelvis during diastole and deflate rapidly and simultaneously during systole. A computer monitors the cardiac cycle via ELECTROCARDIOGRAM (ECG) and coordinates the inflation and deflation of the cuffs accordingly. A therapeutic course involves one hour of EECP daily for 35 hours (typically five days a week for seven weeks), performed at a cardiac clinic or hospital. Most people experience relief from angina for months to 2 or 3 years.

EECP is most appropriate for people who are not receiving adequate relief from medications and would benefit from CORONARY ARTERY BYPASS GRAFT (CABG) but cannot, or choose not, to undergo the surgery. EECP is not appropriate for people who have uncontrolled HYPERTENSION or ARRHYTHMIA or who have bleeding disorders. There are no identified risks associated with EECP. Some people do find the pressure of the counterpulsations somewhat uncomfortable.

See also ANGIOPLASTY; MEDICATIONS TO TREAT CARDIOVASCULAR DISEASE.

fibroelastoma A noncancerous, connective tissue tumor that arises from the ENDOCARDIUM, usually on or near a HEART valve. Also called cardiac papillary fibroelastoma, this rare tumor can become serious or life threatening when it interferes with the function of a heart valve. Fibroelastomas most commonly form on or near the aortic valve or the tricuspid valve. They may become large enough to prevent the valve's proper function or to block the flow of BLOOD through the valve. A fibroelastoma may also create turbulence in the heart, allowing blood to pool and clot. Generally fibroelestomas cause no symptoms and cardiologists may detect them incidentally during echocardiogram for other purposes. Because fibroelastomas pose such a significant risk for clotting and STROKE, cardiologists typically recommend surgery to remove them. Cardiologists do not know what causes fibroelastomas, though there is some debate whether they are congenital or acquired.

See also ANTICOAGULATION THERAPY; OPEN HEART SURGERY; SURGERY BENEFIT AND RISK ASSESSMENT; VALVULAR HEART DISEASE.

gallop A pair of extra HEART SOUNDS the cardiologist can hear with the bell of the STETHOSCOPE during diastole, so-named because they occur in rapid succession and sound like the hooves of a galloping horse. The characteristic sound is that of a deep-toned thud. A gallop often exists with tachycardia (rapid, regular HEART RATE) and generally signals ventricular dysfunction such as might follow HEART ATTACK.

See also ARRHYTHMIA.

heart The organ that pumps BLOOD and maintains circulation. About the size of a closed fist, the heart resides in the chest between the LUNGS, slightly offset to the left behind the protective STERNUM (breastbone). It begins beating at about 3 weeks gestational age and during a typical life time contracts about 2.5 billion times. The heart's four chambers contract in coordinated sequence to pump blood to the lungs and to the body, circulating the body's 5- to 6-liter blood supply through the network of arteries and veins of the cardiovascular system up to three times a minute. Synchronized electrical impulses orchestrate the contractions. One-way valves direct the flow of blood into, through, and out of the heart. The right heart handles deoxygenated blood; the left heart handles oxygenated blood.

HEALTH CONDITIONS THAT CAN AFFECT THE HEART

ANEURYSM	AORTIC STENOSIS
ARRHYTHMIA	ATRIAL FIBRILLATION
BUNDLE BRANCH BLOCK	CARDIAC ARREST
cardiac tamponade	CARDIOMYOPATHY
CONGENITAL ANOMALY	CONGENITAL HEART DISEASE
CORONARY ARTERY DISEASE (CAD)	ENDOCARDITIS
FIBROELASTOMA	HEART ATTACK
HEART FAILURE	HYPERTENSION
LONG QT SYNDROME (LQTS)	MYOCARDITIS
MYXOMA	PALPITATIONS
PAROXYSMAL ATRIAL TACHYCARDIA (PAT)	PERICARDITIS
PREMATURE VENTRICULAR CONTRACTION (PVC)	RHEUMATIC HEART DISEASE
SICK SINUS SYNDROME	TORSADE DE POINTES
	VALVULAR HEART DISEASE

The heart's blood supply comes from the CORONARY ARTERIES, which arise from the root of the AORTA and encircle the heart. The heart has a substantial oxygen appetite; the coronary arteries deliver 20 percent of the body's blood supply and 70 percent of the blood's oxygen content to the heart. The heart is a remarkably sturdy and reliable structure that can withstand significant damage and still function adequately to supply the body's needs for oxygen and other nutrients.

For further discussion of the heart within the context of cardiovascular structure and function, please see the overview section "The Cardiovascular System."

See also LIFESTYLE AND CARDIOVASCULAR HEALTH; RISK FACTORS FOR CARDIOVASCULAR DISEASE.

heart attack The interruption of cardiovascular function. The most common cause of HEART attack is MYOCARDIAL INFARCTION, a blockage of the CORONARY ARTERIES, usually with a BLOOD clot, that disrupts the flow of blood to the heart (MYOCARDIUM). Other causes of heart attack include ARRHYTHMIA, systemic HYPOXIA (such as may occur with drowning or carbon monoxide poisoning), and ELECTROCUTION. About 1.3 million Americans experience heart attacks each year, and 40 percent of them die as a result. Health experts believe significantly more people could survive heart attack with early treatment. Up to 60 percent of people who die from heart attack do so before ever reaching a hospital.

When symptoms suggest heart attack:

- **Call 911**
- **If the person is conscious, have him or her chew an aspirin**
- **If the person is unconscious, has no PULSE or is not BREATHING, begin CARDIOPULMONARY RESUSCITATION (CPR)**
- **Continue CPR until medical help arrives**

When the heart is not beating or cannot beat effectively, oxygen does not get to the body's tissues. Within seconds the body begins to shut down nonessential functions. The BRAIN and the heart itself are the most vulnerable to damage resulting from lack of oxygen; their cells begin to die within three minutes. Immediate CARDIOPULMONARY RESUSCITATION (CPR) can restore OXYGENATION and prevent permanent damage or death. However, the likelihood of survival diminishes by about 10 percent for each minute that passes following the heart's stoppage.

Symptoms and Diagnostic Path

Symptoms vary far more widely than most people realize. The classic symptoms of heart attack are

- intense chest pressure, often crushing
- rapid BREATHING
- profuse sweating (diaphoresis)
- PAIN that radiates from the chest up the left arm
- difficulty breathing or shortness of breath

Many people, and especially women, do not experience classic heart attack symptoms. Instead, their symptoms are more generalized. The danger is that they delay seeking treatment because they are unsure whether they are having a heart attack. Such a delay can be the difference between surviving and dying from a heart attack. Nonclassic heart attack signs include

- NAUSEA and occasionally VOMITING associated with a sense of queasiness
- persistent indigestion (DYSPEPSIA)
- unexplainable anxiety
- vague discomfort in the chest, neck, jaw, or back
- lightheadedness

Warning signs that persist for five minutes require immediate medical assessment. More people survive heart attacks than do not, and more people could survive heart attacks if they received prompt medical treatment. Cardiologists recommend chewing an aspirin tablet at the first signs of possible heart attack, which helps slow the clotting process.

The diagnostic path begins with ELECTROCARDIOGRAM (ECG), which shows the heart's electrical patterns and can usually identify the location of the disrupted function. Regardless of cause, heart attack produces arrhythmias (irregularities of the HEART RATE). Blood tests to measure electrolyte levels and certain proteins that a damaged heart MUSCLE releases also help point to the diagnosis. ECHOCARDIOGRAM can show areas of structural damage to the heart, and CARDIAC CATHETERIZATION with ANGIOGRAM can identify the precise sites of occlusions in the coronary arteries.

Treatment Options and Outlook

Treatment begins with stabilizing the heart's function, which may require various medications including antiarrhythmia medications and drugs that strengthen the heart while reducing the force of its contractions. DEFIBRILLATION may be necessary to restore a functional rhythm to the heart. When doctors can determine within three hours that the cause of the heart attack is a blood clot, they may choose to administer thrombolytic medications ("clot busters") to dissolve the clot as well as anticoagulant medications to prevent further clots. Beyond three hours, thrombolytic medications are not effective. Supportive measures include OXYGEN THERAPY to increase the amount of oxygen in the blood and intravenous fluids to maintain HYDRATION and restore electrolyte balance.

Once the heart recovers, the cardiologist may recommend interventions such as ANGIOPLASTY or CORONARY ARTERY BYPASS GRAFT (CABG) to restore adequate circulation to the heart. Other treatments typically include medications to help regulate the heartbeat and strengthen the heart, and lifestyle modifications for improved cardiovascular health. Treatment also targets any identified underlying causes of the heart attack such as HYPERTENSION (high BLOOD PRESSURE) and ATHEROSCLEROSIS. Current treatment protocols recommend nearly everyone who has a heart attack take statin medications afterward. Statins are lipid-lowering medications that can reduce CHOLESTEROL BLOOD LEVELS, notably low-density lipoprotein cholesterol (LDL-C) by 30 to 40 percent within three months. Statins also help strengthen the heart. Other medications may include beta blockers or calcium channel blockers to lower blood pressure and regulate rhythm.

Depending on the heart attack's severity (the extent of damage to the heart), a person may return to regular activities within a few weeks or require several months to recuperate. Most people benefit from a structured CARDIAC REHABILITATION program.

Risk Factors and Preventive Measures

The primary risk factors for heart attack are CORONARY ARTERY DISEASE (CAD) and hypertension. Many people are unaware that they have either one, so heart attack becomes the first recognition that these conditions exist. Regular ROUTINE MEDICAL EXAMINATION, including tests to measure cholesterol blood levels and blood pressure, help detect these conditions in their early stages, when therapeutic intervention can thwart their progression to life-threatening events such as heart attack and STROKE. Key preventive measures include daily physical exercise, nutritious eating habits, WEIGHT LOSS AND WEIGHT MANAGEMENT, SMOKING CESSATION, and management of conditions such as hypertension and DIABETES.

See also CARDIOVASCULAR DISEASE PREVENTION; LIFESTYLE AND CARDIOVASCULAR HEALTH; MEDICATIONS TO TREAT CARDIOVASCULAR DISEASE; PHYSICAL EXERCISE AND CARDIOVASCULAR HEALTH; ROUTINE MEDICAL EXAMINATION.

heart failure The inability of the HEART to adequately pump BLOOD. Heart failure may affect the right heart (pulmonary circulation), left heart (body circulation), or total heart. Heart failure, occasionally called by its antiquated name dropsy, is a consequence of longstanding CARDIOVASCULAR DISEASE (CVD) that has damaged the structure of the heart. About 5 million Americans live with heart failure.

CONDITIONS THAT CAN CAUSE HEART FAILURE

ATHEROSCLEROSIS	CARDIOMYOPATHY
certain arrhythmias	CONGENITAL HEART DISEASE
CORONARY ARTERY DISEASE (CAD)	HEART ATTACK
HYPERTENSION (high BLOOD PRESSURE)	long-term ALCOHOL abuse
PRIMARY PULMONARY HYPERTENSION	VALVULAR HEART DISEASE

Symptoms and Diagnostic Path

The key symptoms of heart failure are shortness of breath (DYSPNEA) and fluid retention (edema). Because symptoms come on gradually as the heart failure progresses, many people are unaware of them until they notice fatigue, weakness with exertion, rapid or unexplained weight gain, and frequent URINATION. Right heart failure tends to produce peripheral edema (swelling of the lower legs, ankles, and feet). Left heart failure tends to produce central edema (fluid accumulation in the LUNGS), also known as congestive heart failure. Progressive heart failure generally affects the total heart, though right or left failure may be dominant. The diagnostic path typically includes chest X-RAY, which shows fluid accumulation in the lungs and enlargement of the heart, as well as ELECTROCARDIOGRAM (ECG) to assess the heart's electrical activity. Heart failure often causes ARRHYTHMIA. ECHOCARDIOGRAM shows the heart's function and size.

Treatment Options and Outlook

Treatment targets any causative cardiovascular conditions, such as CORONARY ARTERY DISEASE (CAD) and HYPERTENSION. Surgery may correct valve dysfunctions or previously undetected congenital abnormalities such as septal defect. Medications can effectively manage heart failure for many years, allowing people to work and enjoy recreational activities. However, as heart failure progresses, it imposes greater restrictions on physical activity. People who have end-stage heart failure may benefit from a ventricular assist device (VAD), a mechanical pump implanted in the chest cavity that aids the heart in pumping blood. This allows the heart to rest and sometimes to recuperate. The VAD also can serve as a bridge to HEART TRANSPLANTATION, another treatment option for end-stage heart failure.

Risk Factors and Preventive Measures

Underlying cardiovascular conditions are the most important risk factors for heart failure, particularly those that are undiagnosed or poorly managed (notably hypertension and CAD). Lifestyle measures to prevent cardiovascular disease, such as daily physical exercise and not smoking, reduce the likelihood of heart failure as well. CARDIAC REHABILITATION following heart attack can restore heart function to the extent possible. Other preventive measures include careful management of

MEDICATIONS TO TREAT HEART FAILURE

Medication Type	Representative Medications	Effects
angiotensin II receptor inhibitors	losartan, valsartan, telmisartan	dilate arteries; lower BLOOD PRESSURE
angiotensin-converting enzyme (ACE) inhibitors	captopril, enalapril, ramipril, benazepril, monopril	dilate arteries; lower blood pressure; slow progression of HEART FAILURE
anticoagulants	warfarin, heparin, aspirin	reduce blood's tendency to clot
beta blockers	carvedilol, metoprolol, propranolol, sotalol, timolol	regulate HEART RATE
calcium channel blockers	amlodipine	dilate arteries; lower blood pressure
diuretics	hydrochlorothiazide, furosemide, bumetanide, metolazone	reduce fluid accumulations (edema)
inotropics	digoxin, digitoxin	strengthen heart MUSCLE; decrease heart's workload
vasodilators	nitroglycerin, isosorbide, hydralazine, minoxidil	relax and open blood vessels

conditions such as DIABETES and OBESITY (including WEIGHT LOSS AND WEIGHT MANAGEMENT) that can lead to cardiovascular disease.

See also CARDIOVASCULAR DISEASE PREVENTION; MEDICATIONS TO TREAT CARDIOVASCULAR DISEASE; PHYSICAL EXERCISE AND CARDIOVASCULAR HEALTH; VENTRICULAR ASSIST DEVICES (VADS).

heart murmur The sound of BLOOD flowing through an abnormal opening in the HEART. Heart murmur is a sign rather than a condition. Transient heart murmurs are common and benign, generally signaling an occasional or circumstantial incomplete valve closure, and do not require further evaluation or treatment. Transient heart murmurs may be present during FEVER, especially in children, and in pregnant women. Heart murmur sometimes occurs with noncardiovascular conditions such as ANEMIA and HYPERTHYROIDISM.

Murmurs are likely to herald cardiovascular disorders when they appear with symptoms such as shortness of breath (DYSPNEA) with exertion. Persistent heart murmurs may indicate a heart condition that requires treatment. The most common cardiac causes of murmur are

- VALVULAR HEART DISEASE, in which a valve in the heart fails to close properly and blood flows back through it
- atrial septal defect or ventricular septal defect, in which there is an opening in the septum, or heart wall, between the two atria or the two ventricles that allows blood to flow directly between the affected chambers
- AORTIC STENOSIS or pulmonary ARTERY stenosis, in which narrowing of the artery causes blood to back up

Persistent heart murmurs may also be present in GENETIC DISORDERS such as MARFAN SYNDROME or CHROMOSOMAL DISORDERS such as DOWN SYNDROME (trisomy 21). These conditions often have cardiovascular components. The diagnostic path typically includes ELECTROCARDIOGRAM (ECG) and ECHOCARDIOGRAM or COMPUTED TOMOGRAPHY (CT) SCAN and may include more invasive diagnostic procedures such as CARDIAC CATHETERIZATION. Treatment targets the underlying cause of the murmur and may include medications or an OPERATION to repair the problem.

See also OPEN HEART SURGERY; RHEUMATIC HEART DISEASE.

heart rate The number of times in a minute that the HEART completes a CARDIAC CYCLE, commonly measured as the PULSE. At rest, the healthy adult heart beats between 60 and 80 times per minute. The heart rate of a person who is aerobically fit is slower because the heart is more efficient and can pump more blood with each contraction. CARDIOVASCULAR DISEASE (CVD) that reduces CARDIAC CAPACITY often results in an increased heart rate as the heart attempts to compensate for decrease in volume per beat. An unusually rapid heart rate at rest is tachycardia; an unusually slow heart rate at rest is bradycardia. Noncardiac health conditions also can affect heart rate. Heart rate may increase with HYPERTHYROIDISM and decrease with HYPOTHYROIDISM. Other factors that increase heart rate include physical activity, stress, fear, and FEVER.

An aerobically fit heart can increase its pumping volume at a lower increase in heart rate to meet the body's oxygen needs during physical activity or exercise. The heart's maximum heart rate is the upper limit of cardiac function and declines with increasing age. Health experts recommend physical activity for aerobic conditioning that puts the heart rate between 25 and 75 percent of maximum heart rate for 20 to 30 minutes. An individual's target heart rate varies according to AEROBIC FITNESS level. The most effective method for reaching and staying within the target heart rate during exercise is to use a heart monitor, which counts the heartbeats of the person wearing it.

See also AEROBIC EXERCISE; AEROBIC FITNESS; ARRHYTHMIA; EXERCISE AND HEALTH; FITNESS LEVEL; PHYSICAL EXERCISE AND CARDIOVASCULAR HEALTH; WALKING FOR FITNESS.

heart sounds The sounds of the opening and closing of the heart's valves and the passage of BLOOD through them. HEART sounds are an important component of physical diagnosis for cardiovascular conditions. Doctors listen to them using a STETHOSCOPE.

The classic *lubb dupp* sounds are the normal heart sounds in a healthy adult. These are the first and second heart sounds, designated S1 and S2. S1 represents the closing of the tricuspid and mitral valves between the atria and the ventricles. S2 represents the closing of the pulmonary and aortic valves as blood leaves the right and left ventricles, respectively. Other heart sounds are abnormal in adults, occurring only with certain health (and usually heart) conditions. They include

- S3, sometimes called a pericardial knock, indicates a dilated ventricle and ventricular dysfunction such as may occur with CARDIOMYOPATHY (though S3 may be a normal heart sound in young children) or HEART FAILURE. S3 is a low-pitched, vibrational sound the doctor can hear using the bell of the stethoscope.
- S4, indicates abnormal MUSCLE tissue in the heart such as might occur with MYOCARDIAL INFARCTION or hypertrophic cardiomyopathy. S4 also may occur with ISCHEMIC HEART DISEASE (IHD) and HYPERTENSION. Like S3, S4 is a low-pitched vibration the doctor hears with the bell of the stethoscope.
- A click is a high-pitched tone following S1 that indicates improper closing of a valve such as might occur with AORTIC STENOSIS or pulmonary artery stenosis, particularly when these conditions are congenital.
- A snap is a sharp sound following S2 that is typical with mitral stenosis.
- A murmur is a whooshing or whispering sort of sound that indicates blood flowing back through an incompletely closed valve. The timing and quality of the murmur's sound help determine which valve is dysfunctional. Heart murmurs are common and often have no cardiovascular significance, though persistent murmurs may indicate VALVULAR HEART DISEASE.

The cardiologist may choose to further investigate persistent abnormal heart sounds using ELECTROCARDIOGRAM (ECG), ECHOCARDIOGRAM, and other diagnostic procedures depending on the person's symptoms and cardiovascular history.

See also AUSCULTATION; CONGENITAL HEART DISEASE; HEART MURMUR.

heart transplantation The replacement of a diseased HEART with a healthy heart from a deceased donor. Heart transplantation is a therapeutic

option for severe CONGENITAL HEART DISEASE such as hypoplastic left heart syndrome (HLHS) as well as hypertrophic CARDIOMYOPATHY and end-stage HEART FAILURE. South African heart surgeon Christiaan Barnard (1922—2001) performed the first human heart transplantation in 1967, when he replaced the badly diseased heart of 53-year-old Louis Washkansky with the healthy heart of 25-year-old Denise Darvall who died in an accident. Though Washkansky lived only 18 days with the new heart, the OPERATION catapulted cardiovascular medicine into a new era. Today cardiovascular surgeons perform about 2,200 heart transplant operations a year in the United States. More than 70 percent of donor heart recipients live at least 5 years; the longest survival is 24 years.

DONOR HEART SHORTAGE

More than 4,000 people wait on the donor HEART list, yet donor hearts will be available for little over half of them. Many people who could be heart donors are not. Surgeons must place the donor heart in the recipient within four hours of the donor's death. Because many people have not made decisions in advance about organ donation, the time it takes to obtain the family's permission may make it too late to use the heart. There is no cost to the donor's family for removal of donated organs.

Heart transplant recipient criteria Though many people may become critically ill with CARDIOVASCULAR DISEASE (CVD), heart transplantation is a viable option primarily for end-stage heart failure. Health experts estimate that heart transplants could save the lives of 25,000 or more people each year who currently die as a result of heart failure, though the severe shortage of donor hearts restricts heart transplantation to people who are dying from heart failure yet are otherwise healthy—people who have both great need and great potential for survival. Conditions that may result in heart transplantation include

- end-stage heart failure for which medical therapies are ineffective, typically resulting from inoperable CORONARY ARTERY DISEASE (CAD), inoperable VALVULAR HEART DISEASE, and cardiomyopathy
- life-threatening ARRHYTHMIA that does not respond to other treatment
- inoperable congenital malformations of the heart, such as HLHS and tetralogy of Fallot, when surgical reconstruction of the heart either fails or is not likely to be successful

Though numerous clinical criteria establish the severity of cardiovascular status, typically LEFT VENTRICULAR EJECTION FRACTION (LVEF) that falls below 25 percent is the decisive factor. LVEF represents the percent of blood in a full left ventricle that the heart pumps into the body with each contraction of the left ventricle. The amount of blood that enters the body is the stroke volume. A normal LVEF is 55 percent or higher; an LVEF of 40 percent is moderately debilitating. At 25 percent, there are symptoms of cardiovascular distress (such as shortness of breath and ANGINA PECTORIS) even at rest and the person is unable to perform most physical activities.

As well, there are general eligibility criteria to ensure optimal chance for survival after transplantation. These general criteria for heart transplantation include

- expectation of one year or less survival
- age 65 or younger (though an older person who meets all other criteria may be accepted as a recipient)
- otherwise good health
- capable of and willing to comply with lifelong medical care

Various health circumstances tend to preclude consideration for heart transplantation, though they are not absolute. Called comorbid conditions, these include

- INSULIN-dependent DIABETES with NEPHROPATHY, NEUROPATHY, or RETINOPATHY (damage to KIDNEYS, nerves, or eyes)
- primary irreversible kidney disease (not related to cardiovascular disease)
- primary irreversible LIVER disease such as CIRRHOSIS (not related to cardiovascular disease)
- cancer within the previous five years (except SKIN)

- PERIPHERAL VASCULAR DISEASE (PVD) with symptoms such as INTERMITTENT CLAUDICATION
- TRANSIENT ISCHEMIC ATTACK (TIA)
- PRIMARY PULMONARY HYPERTENSION (PPH), CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD), EMPHYSEMA, or severe ASTHMA
- OBESITY

Though none of these criteria is absolute, because of the extreme limited availability of donor hearts cardiologists must be able to justify exceptions. Heart transplantation centers set their own criteria, which may be more or less stringent than the general criteria. Many heart transplantation centers are reluctant to approve individuals who are not likely to maintain the rigorous therapeutic and lifestyle regimens necessary following transplant. In infants and children, heart transplantation is an option for nonsurvivable major congenital anomalies. The shortage of donor hearts severely limits heart transplantation in infants, however.

The donor heart The United Network for Organ Sharing (UNOS) maintains donor lists for all transplant circumstances (except corneas and SKIN) in the United States. UNOS coordinates the acquisition and distribution of donor organs according to strict guidelines and policies that direct available organs to the sickest people on the waiting lists for whom criteria match. Regional transplantation centers carry out the acquisitions and distributions. People waiting for heart transplants must be available 24 hours a day and must be able to reach their transplantation centers within two hours.

The donor's BLOOD TYPE must be the same as the recipient's, and the donor and recipient need to be similar in body size and weight. The heart of a donor who is six feet, four inches tall will not fit in the chest cavity of a recipient who is five feet, three inches tall. Similarly, the heart of a small donor cannot meet the cardiovascular needs of a large recipient. Gender, race, and ethnicity do not matter. The donor's heart must be healthy, and the donor must be under age 65 and free from serious or communicable diseases. Most donor hearts come from people who lose their lives in accidents that cause irreversible, overwhelming BRAIN damage. A specialized surgical team carefully harvests the heart in the operating room, after certifying brain death though while cardiovascular function continues, and places the heart in a cold electrolyte solution to preserve it during transport to the recipient's medical center. The heart remains viable for four to six hours.

Surgical Procedure

The heart transplant operation typically takes three to five hours. The surgeon opens the chest with a large incision lengthwise over the STERNUM and cuts the sternum with a saw to open the chest. After placing the person on CARDIOPULMONARY BYPASS (mechanical oxygenation and circulation of the blood), the surgeon removes the diseased heart. There are several methods for doing this; the most common is to cut away all of the heart except the back walls of the atria to preserve the connections to their blood vessels (the superior VENA CAVA, inferior vena cava, and pulmonary VEIN). Respectively, the surgeons cut away the back of the donor heart to match and suture the donor heart into place beginning with the left atrium. The great arteries—the AORTA and the pulmonary ARTERY—are the final structures the surgeon attaches. The heart spontaneously begins to beat when the surgeon restores blood flow. The surgeon closes the sternum with wire to hold it together while it heals, and closes the outer chest tissues with sutures or staples. Most people remain in the hospital up to 10 days following surgery.

Risks and Complications

Heart transplantation entails numerous risks and complications during (operative) and following (postoperative) the surgery. Operative risks include bleeding, air embolism (air that escapes into the bloodstream from the cardiopulmonary bypass), unexpected anatomic incompatibilities (the donor heart does not "fit"), and inability to restore cardiac function. The most significant complications following heart transplantation, which also account for the greatest number of deaths, are INFECTION and rejection. Arrhythmias and other dysfunctions of the heart sometimes occur, though typically respond to medications. Occasionally the transplanted heart fails to function, a circumstance called graft failure. Immediate retransplantation is generally the only treatment.

People who have transplanted hearts are vulnerable to rapidly progressive CAD, HYPERTENSION, and arrhythmias. The transplanted heart is denervated—though it contains its own conductive NERVE network to convey electrical pacing impulses, it does not have nerves connecting it to the body's sympathetic nerve pathways. Normal NERVOUS SYSTEM mechanisms (the sympathetic nerve pathways) that typically regulate HEART RATE and cardiac workload are not functional in the transplanted heart, though in some people reinnervation occurs over time. The absence of sympathetic nerve pathways also means the person does not experience angina pectoris, a primary symptom of CAD and ISCHEMIC HEART DISEASE (IHD). This increases the risk for silent HEART ATTACK. Cardiologists closely monitor the transplanted heart for any signs of CAD, and also routinely prescribe lipid-lowering medications to help prevent CAD from developing.

Other long-term risks include an increased risk for cancer, most commonly skin and lymphatic, because of the IMMUNOSUPPRESSIVE THERAPY. Infection and rejection remain risks as well. Rejection can be acute (come on suddenly and severely) or chronic (persist in a low-grade fashion over time, or come and go). Many cardiologists believe the accelerated CAD process also results from immunosuppression rather than the conventional factors.

Outlook and Lifestyle Modifications

Most people remain hospitalized for 5 to 10 days after the transplant operation, while the new heart stabilizes and the surgical wounds start to heal. During this time doctors initiate IMMUNOSUPPRESSIVE THERAPY, ANTICOAGULATION THERAPY, and various medications to support the heart's function during early HEALING. All transplant recipients will need to take IMMUNOSUPPRESSIVE MEDICATIONS for the remainder of their lives to prevent their bodies from rejecting the donor organ.

Most heart transplant recipients will continue taking other cardiovascular medications to support cardiovascular efficiency. The transplanted heart's denervation affects its ability to adjust to changing cardiovascular needs in the body, such as with exercise. Many people require a PACEMAKER after transplantation to maintain an adequate heart rate and appropriate heart rhythm. Heart transplantation requires lifetime medical follow-up, usually annual CARDIAC CATHETERIZATION and other diagnostic procedures to assess the heart's function.

Most heart transplant recipients return to their regular work and leisure activities, including sexual activity, gradually over two to three months. The cardiologist may restrict certain kinds of strenuous physical activity depending on the heart's ability to respond to the body's increased oxygen needs. The healing process is generally quite rapid as full cardiovascular function returns the body to its normal function. CARDIAC REHABILITATION helps restore the body to a level of physical STRENGTH and AEROBIC FITNESS that further supports cardiovascular health. Moderate daily physical exercise (such as walking), nutritious eating habits, and total abstinence from smoking are essential.

See also CARDIOVASCULAR DISEASE PREVENTION; MEDICATIONS TO TREAT CARDIOVASCULAR DISEASE; OPEN HEART SURGERY; PHYSICAL EXERCISE AND CARDIOVASCULAR HEALTH; QUALITY OF LIFE; SEXUAL ACTIVITY AND CARDIOVASCULAR DISEASE; TRANSMYOCARDIAL LASER REVASCULARIZATION (TMLR); VENTRICULAR ASSIST DEVICES (VADS).

heredity and heart disease The genetic variables that influence the development of CARDIOVASCULAR DISEASE (CVD). Some forms of cardiovascular disease are entirely hereditary and develop without influence of lifestyle factors. Among them are hypertrophic CARDIOMYOPATHY, LONG QT SYNDROME (LQTS), WOLFF-PARKINSON-WHITE SYNDROME, and familial HYPERLIPIDEMIA. There appear to be few interventions, medical or lifestyle, that can prevent these conditions. Early diagnosis allows for optimal medical management. Researchers suspect that undiagnosed hereditary conditions, notably ARRHYTHMIA disorders, account for up to 25 percent of SUDDEN CARDIAC DEATH in the United States.

Congenital malformations of the HEART often accompany GENETIC DISORDERS or CHROMOSOMAL DISORDERS. Septal defect is common in children who have DOWN SYNDROME (trisomy 21), for example. Most people who have MARFAN SYNDROME, a hereditary connective tissue disorder, have cardiovascular abnormalities including malformed heart valves and arterial walls that lack connective tissue, weakening them and making them vulnerable to ANEURYSM.

As well, there are correlations, though researchers do not fully understand them, among BIRTH DEFECTS involving the heart that occur in conjunction with specific birth defects affecting other body structures. About a third of infants born with ESOPHAGEAL ATRESIA (incomplete formation of the ESOPHAGUS) also have the heart malformation patent ductus arteriosus (PDA). Heart malformations are also common in children who have NEURAL TUBE DEFECTS such as SPINA BIFIDA. These correlations strongly suggest GENE mutations.

Gender and race are other hereditary factors that influence the development of cardiovascular conditions. Men, until about age 60, have three to five times the risk for CORONARY ARTERY DISEASE (CAD) and HYPERTENSION (high BLOOD PRESSURE). Men under age 60 are also more likely to have HEART ATTACK or STROKE. The risk for cardiovascular disease is exponentially higher among African Americans. Hypertension is the leading cause of stroke and kidney failure among African American men between the ages of 35 and 50.

Other forms of cardiovascular disease that tend to "run in the family" may have genetic underpinnings that manifest with interplay from certain lifestyle factors such as cigarette smoking, lack of physical exercise, and eating habits. Such cardiovascular conditions include hypertension (high blood pressure), ATHEROSCLEROSIS, CAD, and PERIPHERAL VASCULAR DISEASE (PVD). Evidence is very strong that appropriate lifestyle interventions can delay or even prevent the onset of such conditions despite any genetic predisposition.

See also CARDIOVASCULAR DISEASE PREVENTION; LIFESTYLE AND CARDIOVASCULAR HEALTH; RISK FACTORS FOR CARDIOVASCULAR DISEASE.

homocysteine An amino acid in the BLOOD that the body's METABOLISM of the essential amino acid methionine produces. (An essential amino acid is one the body cannot synthesize itself but must obtain from dietary sources.) B vitamins and folic acid are necessary to break down homocysteine. Accumulation of homocysteine in the blood circulation appears to accelerate development of ATHEROSCLEROSIS. In the mid-1990s researchers discovered a connection between elevated blood homocysteine levels and early atherosclerosis. Doctors had known since the 1960s of a rare genetic condition, homocystinuria, that caused extensive atherosclerotic disease in teens and young adults. But new research led them to correlate atherosclerosis with elevated homocysteine levels in adults who had no known genetic foundation for them.

Some researchers believe that elevated homocysteine irritates the inside walls of the arteries. The irritation causes INFLAMMATION, which opens the way for ATHEROSCLEROTIC PLAQUE to infiltrate the intima, the innermost layer of the arterial walls. People between the ages of 45 and 60 who have significant atherosclerosis or CORONARY ARTERY DISEASE (CAD) often have elevated homocysteine levels. In people who have elevated homocysteine levels, atherosclerosis may develop more rapidly and at earlier ages. However, research studies as yet have not established a cause and effect relationship between elevated homocysteine and early atherosclerosis.

A blood test can measure the homocysteine level in the blood. Most doctors view homocysteine as a risk factor for CARDIOVASCULAR DISEASE (CVD), though not one that is alone significant enough to cause cardiovascular disease. They recommend people receive the minimum daily amounts of vitamins B_6, B_{12}, and folic acid through dietary sources when possible and with supplements if necessary, as a matter of general health as well as to aid in breaking down homocysteine. People who have elevated homocysteine levels along with other RISK FACTORS FOR CARDIOVASCULAR DISEASE should do what they can to reduce their overall risks, though health experts do not advise folic acid supplementation beyond the recommended intake (400 micrograms daily for an adult) as a preventive measure for cardiovascular health. Adequate folic acid intake appears essential for numerous health reasons, and may help reduce the risks for other health conditions.

See also COENZYME Q10; DIET AND CARDIOVASCULAR HEALTH; NEURAL TUBE DEFECTS.

hyperlipidemia A disorder of lipid METABOLISM, also called hyperlipoproteinemia, that results in abnormally high levels of cholesterol, triglycerides, and lipoproteins in the BLOOD circulation. Hyperlipidemia is a key contributor to ATHEROSCLEROSIS, CORONARY ARTERY DISEASE (CAD), and PERIPHERAL VAS-

CULAR DISEASE (PVD). Hyperlipidemia also can cause health conditions such as PANCREATITIS. Some forms of hyperlipidemia are familial or hereditary and may manifest regardless of lifestyle. Medications can cause hyperlipidemia as well, notably oral contraceptives (birth control pills), estrogen therapy, thiazide diuretics, and corticosteroids. Hyperlipidemia may also be a sign of other health conditions such as CUSHING'S SYNDROME, DIABETES, LIVER dysfunction, and SYSTEMIC LUPUS ERYTHEMATOSUS (SLE). In most people who have hyperlipidemia, however, it appears that lifestyle factors interact with genetics.

Doctors measure lipid levels in the blood and consider them individually as well as in correlation to each other in determining the extent of cardiovascular risk they pose. There are five types, or classifications, of hyperlipidemia that have unique presentations, genetic factors, and characteristic progressions. The five types of hyperlipidemia are

- type I, a rare inherited lipid disorder sometimes called apolipoprotein C-II deficiency, in which very low density lipoprotein (VLDL) triglycerides and lipids called chylomicrons accumulate in the bloodstream
- type II, a common group of familial or acquired lipid disorders, sometimes called hypercholesterolemia, in which low-density lipoprotein (LDL) cholesterol levels in the blood are elevated, and there may be apolipoprotein B deficiency
- type III, an uncommon familial lipid disorder in which VLDL and total cholesterol are elevated, usually resulting from apolipoprotein E deficiency
- type IV, a common familial or acquired lipid disorder in which blood lipid elevations are associated with OBESITY and decline with weight loss
- type V, an uncommon lipid disorder in which triglycerides are extremely elevated, though other blood lipid levels are fairly normal, and that frequently causes pancreatitis

Most forms of hyperlipidemia can occur without evidence of familial or hereditary connections.

Symptoms and Diagnostic Path

Hyperlipidemia itself does not cause symptoms. Doctors detect hyperlipidemia through blood tests, conducted after an 8- to 12-hour fast, that measure blood lipid levels. The pretest fast is important to remove any dietary influences. Elevated blood lipid levels are diagnostic. When blood lipid levels are extremely high and other risks for CARDIOVASCULAR DISEASE (CVD) exist, the doctor may recommend further evaluation to look for CAD, PVD, and other atherosclerotic conditions.

Treatment Options and Outlook

Regardless of the cause of elevated blood lipids, the important therapeutic goal is to reduce them. For people who have mild to moderate elevations and no other cardiovascular disease risk factors (including family history of hyperlipidemia), lifestyle changes alone may be enough to bring lipid levels down to acceptable ranges. Doctors are generally willing to give this approach about two months to lower blood lipid levels. When lipid levels remain elevated despite lifestyle changes, or the person cannot make adequate lifestyle changes, health experts recommend lipid-lowering medications. Lowering blood lipids results in a significant decrease in cardiovascular risk, especially for early CAD and HEART ATTACK (before age 40).

MEDICATIONS TO TREAT HYPERLIPIDEMIA (LIPID-LOWERING MEDICATIONS)

Statins		
atorvastatin (Lipitor)	fluvastatin (Lescol)	lovastatin (Mevacor)
pravastatin (Pravachol)	simvastatin (Zocor)	
Fibrates		
clofibrate (Atromid-S)	fenofibrate (Tricor)	gemfibrozil (Lopid)
Bile acid sequestrants		
cholestyramine (Questran, Prevalite)	colesevelam (WelChol)	colestipol (Colestid)
Selective cholesterol absorption inhibitors		
ezetimibe (Zetia)		

Many doctors recommend niacin, either alone or in combination with lipid-lowering medications, to help lower blood lipid levels. Niacin

decreases the liver's production of VLDL and low-density lipoprotein (LDL), which curtails triglyceride production. Niacin can cause unpleasant facial flushing and tingling sensations in the fingers and toes, however, even at low doses.

Risk Factors and Preventive Measures

The key risk factors for hyperlipidemia are family history and lifestyle habits. Most people can lower their risk for hyperlipidemia through eating habits and exercise. Even in combination with medication, lifestyle factors are important for maintaining healthy lipid metabolism.

See also CARDIOVASCULAR DISEASE PREVENTION; CHOLESTEROL BLOOD LEVELS; CHOLESTEROL, ENDOGENOUS; C-REACTIVE PROTEIN; TRIGLYCERIDES, BLOOD LEVEL; XANTHOMA.

hypertension BLOOD PRESSURE that remains consistently elevated. Health experts estimate that 25 percent of American adults—about 75 million people—have hypertension, though about half of them do not know it. Hypertension, also called high blood pressure, is a leading cause of STROKE and KIDNEY disease, and a key factor in many heart attacks.

Stroke kills nearly 150,000 Americans each year, making it the third leading cause of death in the United States, and disables about a million others. Yet as many as 80 percent of strokes are preventable through controlling blood pressure. Early diagnosis of hypertension to prevent stroke is a goal of the U.S. preventive health initiative HEALTHY PEOPLE 2010.

Loss of feeling or movement and blurred or dimmed vision, especially on only one side of the body, and difficulty forming or understanding words, are early warning signs of STROKE that require emergency medical evaluation.

Hypertension has numerous effects on the cardiovascular system, and over time alters the function of the HEART as well as the distribution of blood throughout the body. Hypertension in combination with ATHEROSCLEROSIS, the most common form of CARDIOVASCULAR DISEASE (CVD) in the United States, can be particularly damaging or lethal. In combination with DIABETES, hypertension significantly raises the risk for kidney failure and RETINOPATHY of diabetes, in which the tiny blood vessels in the RETINA rupture, causing blindness.

Symptoms and Diagnostic Path

Hypertension has no symptoms, which is why regular blood pressure monitoring is so important. For many people, the first indication of hypertension is stroke or kidney disease, the two leading complications of hypertension. Hypertension may also trigger HEART ATTACK. Occasionally people who have severely elevated blood pressure experience headaches.

Healthy blood pressure is a systolic reading below 120 millimeters of mercury (mm Hg) and a diastolic reading below 80 mm Hg. Persistent readings above these levels for either systolic or diastolic pressure constitute hypertension. Generally the doctor takes several blood pressure readings at different times of the day over a span of time before diagnosing hypertension. A diagnosis of hypertension follows a minimum of three elevated readings. Many people are anxious or nervous when visiting the doctor, sometimes resulting in a phenomenon doctors call "white coat hypertension." An assessment of vital signs, including blood pressure, usually takes place at the start of the health-care visit; when blood pressure is elevated, the doctor may take a measurement again at the end of the visit when the person's anxiety level has dropped.

HYPERTENSION CLASSIFICATIONS

Classification	Systolic	Diastolic
Prehypertension	120–139 mm Hg	80–89 mm Hg
Stage 1 hypertension	140–159 mm Hg	90–99 mm Hg
Stage 2 hypertension	160 mm Hg and above	100 mm Hg and above

Treatment Options and Outlook

Lifestyle modification is the first and the foundational treatment approach for hypertension. Intervention at the prehypertension level can bring blood pressure under control before it becomes a health problem. Overweight or OBESITY causes or exacerbates much hypertension, so often the doctor's first recommendation is weight loss through increased physical activity and changes in eating habits that reduce overall caloric intake. Further dietary modifications often include reducing

sodium consumption, as high amounts of dietary sodium cause the body to maintain fluid. This increases blood volume and, correspondingly, blood pressure. Doctors also recommend reducing dietary fat, especially saturated fat, and cholesterol to reduce the risk for HYPERLIPIDEMIA and atherosclerosis. Atherosclerosis narrows and stiffens the arteries, increasing the resistance blood encounters, and is a significant factor in hypertension.

The mainstay of treatment for hypertension is medication. There are numerous classifications and kinds of drugs that can lower blood pressure through different actions and mechanisms. Often the doctor will combine medications in a multifaceted approach. Many of the medications used to treat hypertension also treat other cardiovascular conditions. Cardiologists often prescribe beta blockers and calcium channel blockers, for example, to treat ARRHYTHMIA, CARDIOMYOPATHY, and HEART FAILURE. Because cardiovascular disease is often a constellation of conditions, this is an effective approach for preventing further cardiovascular disease from developing.

The decision to begin medication for hypertension depends on the blood pressure elevation and other cardiovascular disease or risk factors. Doctors may choose to initiate antihypertensive medication therapy for stage 1 hypertension in people who have multiple cardiovascular risks, yet try three to six months of lifestyle modification for people who have few or no other known cardiovascular risks. Medication needs may change if other health conditions develop or cardiovascular status changes. On the positive side, lifestyle modifications in combination with medication therapy often can reduce or eliminate the need for medication in people who have stage 1 hypertension and occasionally in people who have stage 2 hypertension.

KINDS OF MEDICATIONS TO TREAT HYPERTENSION

angiotensin II receptor blockers (ARBs)	angiotensin-converting enzyme (ACE) inhibitors
beta blockers	calcium channel blockers
diuretics	vasodilators

Risk Factors and Preventive Measures

The leading risk factors for hypertension are age, cigarette smoking, dietary habits, and physical inactivity. Health conditions such as obesity, diabetes, and atherosclerosis further increase the risk for hypertension. Health experts recommend all adults over age 40 undergo annual blood pressure screening, with more frequent screening for people who have increased risk. Daily physical exercise such as walking helps control weight as well as maintain cardiovascular efficiency, reducing risk across the spectrum of cardiovascular disease.

See also CARDIOVASCULAR DISEASE PREVENTION; DIET AND CARDIOVASCULAR HEALTH; LIFESTYLE AND CARDIOVASCULAR HEALTH; PHYSICAL EXERCISE AND CARDIOVASCULAR HEALTH; SMOKING CESSATION.

hypotension Below-normal BLOOD PRESSURE. Hypotension is most often a SIDE EFFECT of medications, a complication of HEART ATTACK, the result of significant BLOOD loss, or a component of cardiovascular SHOCK. Factors that decrease the flow of blood through the body typically result in reduced blood pressure. Idiopathic hypotension (hypotension that exists without apparent cause) often suggests a neurologic cause that reflects damage to the brainstem or HYPOTHALAMUS. STROKE that interrupts blood flow to these parts of the BRAIN may be accountable, interfering with the body's blood pressure regulation mechanisms.

Hypotension is a frequent side effect of many MEDICATIONS TO TREAT CARDIOVASCULAR DISEASE, among them diuretics, antihypertensives (drugs to lower blood pressure), and alpha blockers (drugs to lower blood pressure or treat ARRHYTHMIA). Cardiovascular conditions that reduce CARDIAC OUTPUT (the heart's ability to pump an adequate volume of blood to meet the body's OXYGENATION needs) are common causes of hypotension. Such conditions include severe dilated CARDIOMYOPATHY, advanced HEART FAILURE, bradycardia and other arrhythmias that slow the heart, AORTIC STENOSIS, and unrecognized HEART ATTACK. Hypotension, notably postural hypotension (a sudden drop in blood pressure upon arising), may be a symptom of ADDISON'S DISEASE, an autoimmune disorder that destroys the ADRENAL GLANDS. The adrenal glands produce the key hormones that increase blood pressure, ALDOSTERONE, EPINEPHRINE, and NOREPINEPHRINE.

The most common symptoms of hypotension are lightheadedness and SYNCOPE (fainting), especially when rising from sitting or lying down. The

normal pull of gravity causes blood to temporarily pool in the large veins of the legs. Any lapse between the change of position and the signals that activate the body's blood pressure regulation mechanisms, results in an inadequate blood supply to the brain that causes loss of consciousness. Syncope following meals, called postprandial syncope, also is common, as the body draws an increased blood volume to the gastrointestinal tract to support the functions of digestion. The diagnostic path typically includes review of medications the person is taking as well as blood tests to measure levels of the adrenal hormones, blood electrolytes, and blood composition. Treatment depends on the underlying cause. When the cause is medication, changing the DOSE or switching to a different medication often remedies the hypotension. Neurologic and endocrine causes may require more extensive diagnostic evaluation and comprehensive treatment approaches.

See also ADRENAL INSUFFICIENCY; AUTOIMMUNE DISORDERS; HORMONE; PHEOCHROMOCYTOMA.

I

implantable cardioverter defibrillator (ICD) A small, battery-operated electronic device, similar to a PACEMAKER, that monitors the heart's electrical activity for certain patterns of ARRHYTHMIA and administers a moderate electrical shock when the HEART stays in the pattern beyond the programmed length of time. One or two wires, called leads, extend from the ICD's PULSE generator to the interior of the heart, threaded through a BLOOD vessel during a procedure similar to a CARDIAC CATHETERIZATION. The cardiologist creates a small pocket in the tissues near the shoulder or in the abdomen to implant the pulse generator, a tiny computer. Once placed, the leads and the ICD are permanent. The cardiologist then programs the ICD to maintain the appropriate heart rhythm.

ICD is a treatment option for ventricular tachycardia and VENTRICULAR FIBRILLATION, arrhythmia disorders that affect the ability of the ventricles to contract to expel blood from the heart. Ventricular tachycardia, in which the ventricles contract rapidly but regularly, is exhausting for the heart and does not generate adequate CARDIAC OUTPUT to meet the body's needs. Ventricular fibrillation, in which the ventricles contract rapidly and irregularly, is life-threatening. An ICD can initiate pacing impulses when the heart's rate becomes too slow or a stronger electrical impulse to shock the heart from a harmful to a normal rhythm (CARDIOVERSION). Most people do not feel the pacing impulses though do feel a jolt with cardioversion impulses. People who have ICDs need to be cautious around electrical devices because they generate magnetic fields that can interfere with an ICD's operation and programming.

See also CARDIAC RESYNCHRONIZATION THERAPY (CRT); MEDICATIONS TO TREAT CARDIOVASCULAR DISEASE; RADIOFREQUENCY ABLATION.

intermittent claudication PAIN in the lower legs that occurs with physical activity such as walking. Intermittent claudication is the primary symptom of PERIPHERAL VASCULAR DISEASE (PVD), which is ATHEROSCLEROSIS that affects the arteries of the legs. The atherosclerotic accumulations of PVD occlude (block) BLOOD flow through the arteries, limiting their ability to respond to the increased oxygen need of the leg muscles during exercise. The insufficient oxygen causes pain that is typically severe enough to stop the activity. Resting relieves the pain and the person can resume the activity.

People who have intermittent claudication typically develop a pattern of walking and resting that accommodates their symptoms. About 60 percent of people who have intermittent claudication have it in both legs. Cigarette smoking, DIABETES, and lack of physical exercise are the leading causes of PVD and intermittent claudication. The PVD that causes intermittent claudication most often affects the popliteal ARTERY, which branches from the femoral artery and drops behind the knee to supply the lower leg with blood.

The most effective treatment is consistent exercise such as walking. Doctors recommend a progressive approach that begins with walking until pain forces rest, several times every day, and trying to extend the time by a few minutes every week. The regular physical activity conditions the leg muscles, improving the efficiency with which they use oxygen and decreasing oxygen demand. Most people who have PVD and intermittent claudication also take medications to decrease the blood's clotting tendencies, such as ASPIRIN THERAPY or anticoagulation medications such as clopidogrel (Plavix) or warfarin (Coumadin). These methods cannot eliminate intermittent claudication though they can reduce its severity.

See also CARDIOVASCULAR DISEASE PREVENTION; COAGULATION; CORONARY ARTERY DISEASE (CAD); DEEP VEIN THROMBOSIS (DVT); MEDICATIONS TO TREAT CARDIOVASCULAR DISEASE; MUSCLE.

intra-aortic balloon pump (IABP) counterpulsation A method to relieve strain on the HEART when there is significant damage to the heart such as after a major HEART ATTACK, in end-stage HEART FAILURE while awaiting HEART TRANSPLANTATION, or in cardiovascular SHOCK. Such circumstances result in the heart being unable to pump enough BLOOD to meet the body's needs. IABP counterpulsation helps pull blood through the AORTA, assisting the left ventricle's pumping efforts.

The cardiologist inserts the IABP on the tip of a catheter during a CARDIAC CATHETERIZATION, threading it through a small incision in a major peripheral ARTERY near the surface of the SKIN, such as the femoral artery in the groin or the brachial artery in the upper arm. The IABP rests in the root of the aorta, its inflated balloon cuff holding it firmly in place. An inner ringlike balloon forms the inside channel of the IABP, inflating and deflating in synchronization with the CARDIAC CYCLE. The channel narrows as the IABP inflates during diastole (filling of the ventricles) and widens as the AIBP deflates during systole (contraction of the ventricles). The effect is to pull blood into the aorta at the same time the left ventricle pumps blood out, easing the amount of pressure necessary to move the blood. A computer closely monitors the heart's electrical patterns to precisely time the inflation and deflation of the IABP's inner balloon.

See also ENHANCED EXTERNAL COUNTERPULSATION (EECP).

ischemic heart disease (IHD) The consequential condition that results when CORONARY ARTERY DISEASE (CAD) and other conditions that affect the heart's blood supply deprive the HEART of oxygen over an extended period of time. Ischemia is the medical term for a temporary interruption of BLOOD flow; in ischemic heart disease (IHD), the interruptions are temporary but recurrent. Cardiac ischemia occurs when the CORONARY ARTERIES are unable to provide the heart with enough blood to meet its oxygen needs. Coronary artery spasm, which often occurs with moderate to advanced CAD, also can generate ischemic episodes.

Ischemia often results in a specific kind of discomfort or PAIN, ANGINA PECTORIS. However, many people who have IHD have what doctors call silent ischemia that causes no symptoms until HEART ATTACK, and sometimes not even then. Silent heart attack can further contribute to the IHD when parts of the heart MUSCLE are no longer functional. IHD may alternately improve and worsen according to the person's activity level, as the heart's oxygen needs increase with activity.

The diagnostic path seeks to identify the underlying condition of the symptoms, which is usually CAD though sometimes ARRHYTHMIA disorders are to blame. Treatment targets the causative condition, and may include ANGIOPLASTY or CORONARY ARTERY BYPASS GRAFT (CABG) as well as medications to regulate the heart's rate and workload. Ischemic heart disease generally improves with these measures.

See also ATHEROSCLEROSIS; CARDIOVASCULAR DISEASE PREVENTION; LIVING WITH CARDIOVASCULAR DISEASE; TRANSMYOCARDIAL LASER REVASCULARIZATION (TMLR).

Kawasaki disease An acute condition affecting children that can weaken the CORONARY ARTERIES and other cardiovascular structures, resulting in HEART ATTACK, ANEURYSM, or permanent damage. Kawasaki disease, also called mucocutaneous LYMPH NODE syndrome, comes on suddenly with RASH, FEVER, CONJUNCTIVITIS, and swollen lymph nodes (LYMPHADENOPATHY). The characteristic symptom that raises suspicion the condition is more than a typical viral INFECTION is the bright red color of the lips and mucous membranes in the MOUTH. After about five days the palms of the hands and soles of the feet also become bright red. The child appears, and is, very ill. The acute phase of the disease runs about three weeks. The diagnostic path is primarily clinical; there are no definitive tests for Kawasaki disease.

Treatment during the acute phase includes efforts to keep the child comfortable as well as administering high-DOSE aspirin. Aspirin, not usually given to children who have fevers because of the risk for REYE'S SYNDROME, is the treatment of choice for Kawasaki disease because it not only reduces FEVER but also reduces cardiovascular INFLAMMATION and has antiplatelet action that helps prevent blood clots from forming. These effects lower the likelihood of cardiovascular damage or crisis. Intravenous IMMUNOGLOBULIN, which delivers generalized antibodies that aid the body's IMMUNE RESPONSE, given early in the course of the disease seems to mitigate symptoms in some children.

Sometimes cardiovascular symptoms manifest during the disease's acute phase, though typically it is months to years later that problems become apparent. Doctors recommend cardiovascular assessment, including ELECTROCARDIOGRAM (ECG) and ECHOCARDIOGRAM, for children at the time of diagnosis. Detected cardiovascular changes require regular followup, with treatment as necessary. The most serious long-term consequences of Kawasaki disease are aneurysms of the coronary arteries that cause heart attack. In some children, inflammation attacks the heart valves, resulting in VALVULAR HEART DISEASE that requires ongoing medical attention and sometimes heart valve replacement in adulthood.

Doctors believe an infectious agent, such as a VIRUS, likely causes Kawasaki disease though as yet researchers have been unable to isolate it. Though occasionally there appear to be clusters of Kawasaki disease, the condition does not appear to be contagious through contact among family members and close contacts. Children under five years of age are most likely to develop Kawasaki disease. Children who have had Kawasaki disease rarely get it again.

See also ANTIBODY; SCARLET FEVER; TOXIC SHOCK SYNDROME.

L

left ventricular ejection fraction (LVEF) The percent of BLOOD a full left ventricle pumps into the AORTA with each CARDIAC CYCLE. LVEF provides an assessment of cardiovascular limitations resulting from damage to the HEART such as by MYOCARDIAL INFARCTION or HEART FAILURE. Normal LVEF is 55 percent; LVEF below 35 percent indicates severe heart failure. Because it is not possible to directly measure the volume of blood the left ventricle pumps, cardiologists use indirect methods to calculate the LVEF. Among these methods are ECHOCARDIOGRAM with Doppler ULTRASOUND, radionuclide scans, and MAGNETIC RESONANCE IMAGING (MRI), all of which allow the cardiologist to mathematically determine the volume of the ventricle and visualize the flow of blood through the heart. LVEF is one method to monitor the progression of a degenerative cardiovascular condition such as heart failure as a criterion for HEART TRANSPLANTATION.

See also CARDIAC CAPACITY; CARDIAC OUTPUT.

lifestyle and cardiovascular health The variables of daily living and the effects they have on the health of the HEART and BLOOD vessels. Health experts estimate that lifestyle modifications alone could eliminate 90 percent or more of acquired CARDIOVASCULAR DISEASE (CVD). Given that 60 million Americans currently have at least one form of cardiovascular disease, the potential impact of such a reduction on LIFE EXPECTANCY as well as QUALITY OF LIFE is overwhelming. The three lifestyle factors that most significantly influence cardiovascular health are cigarette smoking, dietary habits, and physical activity.

Cigarette Smoking

NICOTINE, the active ingredient in cigarette smoke, is a potent vasoconstrictor and cardiovascular stimulant. Before a smoker finishes the first inhalation from a cigarette, nicotine is already surging through the bloodstream. It causes blood vessels throughout the body to stiffen and narrow, raising BLOOD PRESSURE. It raises the HEART RATE, further increasing blood pressure as well as the heart's workload. Simultaneously, other substances in cigarette smoke interfere with the OXYGEN–CARBON DIOXIDE EXCHANGE in the LUNGS, reducing the amount of oxygen the blood carries into the blood circulation. As smoking continues over time, nicotine causes physical changes in the cells of the ARTERY walls, reducing their ability to contract and relax. Blood pressure elevation may become permanent (HYPERTENSION), and the arteries are more susceptible to ATHEROSCLEROTIC PLAQUE. With SMOKING CESSATION much of the arterial function returns. Hypertension may improve though ATHEROSCLEROSIS, including CORONARY ARTERY DISEASE (CAD) and PERIPHERAL VASCULAR DISEASE (PVD), remains.

Dietary Habits

The foods and the quantities of them that a person eats significantly influence blood levels of cholesterol and triglycerides. A diet high in fruits, vegetables, and whole grain products provides a rich source of vitamins, antioxidants, and fiber that help regulate these lipids. This is important because elevated blood lipids (HYPERLIPIDEMIA) form the basis of atherosclerosis and the conditions that result, notably hypertension, CAD, and PVD. These nutrients also help the body tissues, including those of the cardiovascular system, to function efficiently. Nutritious eating further helps regulate the body's GLUCOSE–INSULIN balance, important from a cardiovascular perspective because insulin plays a key role in the kinds and amounts of cho-

lesterol and lipoproteins the LIVER manufactures. Insulin is also a key player in type 2 DIABETES, which is another risk factor for cardiovascular disease. Eating too much of any kind of food, however, results in increased body weight. OBESITY is another risk factor for numerous forms of CVD, notably hypertension and atherosclerosis. For many people a weight loss of 10 pounds can decrease systolic blood pressure by 10 millimeters of mercury (mm Hg) and lower CHOLESTEROL BLOOD LEVELS by 5 to 10 percent.

Physical Exercise

Daily physical activity is emerging as perhaps the single-most important lifestyle factor in regard to cardiovascular health and perhaps health overall. Exercise affects cellular METABOLISM in numerous ways. Cardiovascularly, exercise improves the efficiency with which cells use oxygen, lowering demand on the heart. AEROBIC EXERCISE increases LUNG CAPACITY, putting more oxygen into the blood with each breath. Exercise also increases insulin sensitivity, improving cholesterol ratios as well as glucose efficiency. Walking aids the lower extremities in moving blood back to the heart, with the skeletal muscles massaging and supporting the veins that must work against gravity to accomplish this task.

Lifestyle Modifications

Health experts agree that while the greatest cardiovascular benefits come from lifelong lifestyle habits that support cardiovascular health, it is never too late to make changes that improve cardiovascular status. Even when cardiovascular disease exists, doing lifestyle modifications such as nutritious EATING HABITS, daily physical exercise, WEIGHT LOSS AND WEIGHT MANAGEMENT, and SMOKING CESSATION can mitigate symptoms and allow a more acceptable quality of life.

See also CARDIOVASCULAR DISEASE PREVENTION; DIET AND CARDIOVASCULAR HEALTH; DIET AND HEALTH; EXERCISE AND HEALTH; HEALTH RISK FACTORS; HEALTHY PEOPLE 2010; PHYSICAL EXERCISE AND CARDIOVASCULAR HEALTH; SMOKING AND CARDIOVASCULAR DISEASE.

living with cardiovascular disease More than 70 million Americans—nearly 35 percent of the U.S. population—live with some form of diagnosed CARDIOVASCULAR DISEASE (CVD). Many of them continue in the jobs and leisure activities they have always enjoyed, due in large part to advances in technology, surgery, and drugs that allow early diagnosis, prompt intervention, and successful treatment. Others—about 10 million—find their lives entirely changed by permanent disability. STROKE alone disables nearly a million Americans each year. Some people see their cardiovascular conditions as opportunities to improve their health and QUALITY OF LIFE, and some people see them as limitations. Living with CVD has physical and emotional dimensions that reach into nearly every aspect of life, from work and career to relationship and family.

Physical Dimensions

About 10 million Americans live with some degree of permanent disability as a result of CVD that limits their abilities to work and participate in activities they enjoy. One in three people who has a stroke experiences residual complications ranging from memory and cognitive disturbances to PARALYSIS. Half of people who have heart attacks experience compromised cardiovascular function, some of which is short term and improves over time, and some of which is long term and does not get much better with time. These changes may require adaptive accommodations in the home and the workplace. CARDIAC REHABILITATION programs help people recover to the best level possible, teaching new methods for managing lifestyle tasks and establishing individual recovery goals and the steps to reach them.

Emotional Dimensions

People who experience heart attack and other cardiovascular crises find themselves confronting their own mortality in ways that can be disconcerting and frightening. Some people experience renewed appreciation for life and its daily details. Some people turn to faith, either in gratitude or in anger. Some people flail about emotionally, suddenly unsure of life's purpose. Family members may not understand or may themselves find the close call a frightening experience. Feelings and emotions are as much a part of managing cardiovascular conditions as are medications and operations. Medical centers and hospitals that provide

cardiovascular care typically sponsor support groups where people can share their worries and fears.

Outlook

In the course of 40 years—the span of a generation—cardiovascular disease shifted from harbinger of restricted living and early death to a plethora of treatment options. For many people, living with cardiovascular disease is little different from living without cardiovascular disease. Operations, medications, and lifestyle interventions can mitigate many forms of cardiovascular disease. With the intensified focus on preventive measures and interventions, the generation born at the turn of the 21st century could be the first that does not have the experience of living with cardiovascular disease.

See also CARDIOVASCULAR DISEASE PREVENTION; LIFESTYLE AND CARDIOVASCULAR HEALTH; RISK FACTORS FOR CARDIOVASCULAR DISEASE.

long QT syndrome (LQTS) An ARRHYTHMIA disorder in which an electrical conduction defect in the HEART results in delayed repolarization of myocardial cells. Repolarization is the process by which myocardial cells restore themselves to receive another electrical impulse. With LQTS, the myocardial cells hold a positive charge much longer than normal, preventing the heart from recharging for the next CARDIAC CYCLE. Most LQTS is hereditary, and researchers have isolated a number of GENE mutations that affect the heart's ion channels (conductive pathways), usually potassium channels though sometimes sodium channels. The condition can also develop as a consequence of STROKE or as a medication SIDE EFFECT, notably with antiarrhythmia and ANTIDEPRESSANT MEDICATIONS though numerous drugs affect the QT interval.

The points Q and T on the ELECTROCARDIOGRAM (ECG) identify polarization or discharge of electrical activity (the Q wave) and repolarization (the T wave). Doctors call the amount of time it takes for this phase to complete the QT interval. The longer the QT interval, the greater the risk for a dangerous arrhythmia called TORSADE DE POINTES, a form of highly unstable ventricular tachycardia (rapid though regular contractions of the ventricles, typically exceeding 100 contractions a minute). Torsade de pointes can quickly lead to VENTRICULAR FIBRILLATION, in which the ventricular contractions are rapid, irregular, and nonfunctional. Ventricular fibrillation quickly becomes life-threatening and may require emergency DEFIBRILLATION. LQTS is a common cause of SUDDEN CARDIAC DEATH in young people who are apparently healthy.

Symptoms and Diagnostic Path

Often, people who have LQTS do not have symptoms, and doctors detect the condition during ECG done for other reasons. The most common symptom that does occur is unexplained syncope (fainting), especially with intense exercise or emotional response (such as anger or fear). ECG generally provides the diagnosis, though the cardiologist may do an exercise STRESS TEST to evaluate the heart's electrical response with increased physical activity.

Treatment Options and Outlook

The standard medical treatment for LQTS is a beta blocker medication, which helps slow and stabilize the HEART RATE. The beta blockers most commonly prescribed for LQTS are propanolol (Inderal), metoprolol (Lopressor or Toprol), nadolol (Corgard), and atenolol (Tenormin). Beta blockers control LQTS in about 70 percent of people who have the condition. When medications fail to prevent arrhythmias, the next level of treatment is an IMPLANTABLE CARDIOVERTER DEFIBRILLATOR (ICD), an electronic device similar to a PACEMAKER. The ICD monitors the heart's rhythm and can deliver an electrical shock to return the heart to a normal rhythm should dangerous arrhythmias occur.

Because a prolonged QT interval is most likely to occur during intense physical exercise that puts high demand on the heart LQTS may require lifestyle modifications, especially for people who participate in competitive sports. Most people are able to enjoy recreational athletic and physical activities, however.

Risk Factors and Preventive Measures

Gene mutations establish the foundation for LQTS, probably even in secondary LQTS (LQTS

that results as a side effect of medication or other events). Family history of LQTS or sudden cardiac death is an important diagnostic clue. When LQTS is secondary, removing the cause often ends the conductive irregularities. There are no known preventive measures for primary LQTS. Treatment often controls symptoms and prevents life-threatening arrhythmia.

See also CARDIAC ARREST; MEDICATIONS TO TREAT CARDIOVASCULAR DISEASE; TAMPONADE, CARDIAC.

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medications to treat cardiovascular disease Drugs that alter the function of the HEART or the BLOOD vessels. Plants provided the earliest forms of DRUG therapy for heart problems. Healers in ancient Egypt and Greece brewed teas of foxglove leaves, the source of digitalis, to slow a rapid heartbeat and strengthen a weakened heart. By the 17th century physicians were using a relatively standardized formulation of powdered foxglove to treat congestive HEART FAILURE. Foxglove leaves remain the source from which laboratories extract digitalis to manufacture digoxin and digitoxin, the digitalis-based medications that remain in use today. Quinidine, a medication to treat ARRHYTHMIA (irregular heartbeat), derives from the bark of the South American *Cinchona ledgeriana* tree (also the original source of the antimalarial drug quinine). Scientists isolated quinidine as an extract to treat ATRIAL FIBRILLATION in 1918. *Rauwolfia serpentina* was a staple in the PHARMACOPOEIA of healers in ancient India, who used its dried roots to lower BLOOD PRESSURE. The antihypertensive medication reserpine, which debuted in the 1950s, contains *Rauwolfia* alkaloid extracts. Today medications are the mainstay of treatment for most forms of CARDIOVASCULAR DISEASE (CVD), though most are synthetic formulations that come from the laboratory.

Cardiovascular disease often involves multiple, interrelated components. HYPERTENSION (high blood pressure) often arises from underlying ATHEROSCLEROSIS, the most common cardiovascular disease. CORONARY ARTERY DISEASE (CAD), a manifestation of atherosclerosis that affects the CORONARY ARTERIES supplying the heart, may generate arrhythmias and ANGINA PECTORIS. Heart failure typically features numerous symptoms arising from a constellation of cardiovascular dysfunctions. The recent direction of research has correspondingly produced medications that treat the constellation, not just a single symptom. A calcium channel blocker, a classification of medication that debuted in the 1990s, dilates peripheral arteries, and slows the HEART RATE; these actions lower blood pressure, regulate the heart's rhythm, and strengthen the heart's pumping action. Combining medications often produces more effective results. For example, the cardiologist may also prescribe a diuretic to extract additional fluid from the body, which lowers blood volume and thus blood pressure, which in turn relieves the heart's workload to reduce heart failure. The combination of the diuretic and the calcium channel blocker may restore nearly normal cardiovascular function.

People respond differently to cardiovascular drugs, even when they have the same diagnoses. It may take a trial and error period to find the right medication or combination of medications for each individual. Cardiovascular medications may interact or interfere with each other, with medications for other health conditions, with herbal preparations, and with certain foods. For example, grapefruit (whole fruit or juice) interferes with the actions of calcium channel blockers, statin lipid-lowering medications, digoxin, potassium channel blockers, and warfarin. The herb GOLDENSEAL, taken to enhance immune function, elevates blood pressure and interacts with antihypertensive medications. Dark green leafy vegetables contain VITAMIN K, which increases clotting and interferes with anticoagulant medications.

Most medications to treat cardiovascular conditions have the potential for side effects, some of which may be life-threatening. Sodium channel and potassium channel blockers, digoxin, warfarin, and heparin all are NARROW THERAPEUTIC INDEX (NTI) drugs, for which the margin between

helpful and harmful is exceedingly thin. These drugs have the potential to create life-threatening arrhythmias. Other cardiovascular medications may cause symptoms such as COUGH, HEADACHE, ERECTILE DYSFUNCTION, tiredness, CONSTIPATION, dizziness, flushing, and edema (swelling, particularly of the ankles and wrists). It is important for people to know what side effects are possible with they medications they are taking and to notify the doctor if any of them occur. Though some side effects are common to all of the drugs within a classification, sometimes switching to a different medication within the same classification eliminates the troublesome side effect.

ACE Inhibitors

Angiotensin-converting enzyme (ACE) inhibitors block the action of angiotensin-converting enzyme (ACE). Angiotensin II is a potent vasoconstrictor that raises blood pressure. Blocking the conversion of its precursor, angiotensin I (angiotensinogen), prevents these events and lowers blood pressure. ACE inhibitors also have a mild to moderate diuretic effect, further lowering blood pressure by reducing blood volume.

Pregnant women should not take ACE inhibitors during the second and third trimesters of PREGNANCY, as these drugs may cause harm or death to the fetus.

Doctors prescribe ACE inhibitors as first-line treatment, usually in combination with diuretics, to treat hypertension and heart failure and to reduce the risk of subsequent heart attacks after an initial heart attack. Some ACE inhibitor products combine an ACE inhibitor with a diuretic.

COMMON ACE INHIBITORS

benazepril (Lotensin)	captopril (Capoten)
enalapril (Vasotec)	fosinopril (Monopril)
lisinopril (Prinivil, Zestril)	moexipril (Univasc)
perindopril (Aceon)	quinapril (Accupril
ramipril (Aceon (Altace)	trandolapril (Mavik)

Among the common side effects are HEADACHE, gastrointestinal upset, dizziness, SKIN RASH or skin sensitivity to sunlight, and fatigue. ACE inhibitors have a propensity to cause a dry, nonproductive cough; though annoying, the cough is benign and typically goes away within two months of stopping the medication.

Adenosine

Adenosine is an intravenously administered medication that momentarily interrupts the flow of the heart's electrical pacing signals, creating an "electrical short" of sorts that very briefly stops the heart. It is a treatment for PAROXYSMAL ATRIAL TACHYCARDIA (PAT), also called paroxysmal supraventricular tachycardia (PSVT), that converts the heart to normal sinus rhythm. Sometimes cardiologists refer to this treatment as chemical or pharmaceutical CARDIOVERSION. Adenosine is available in the United States as the brand name product Adenocard. The effects of adenosine last only one to two minutes. Side effects may include headache, lightheadedness, NAUSEA, and shortness of breath (DYSPNEA). Adenosine also may trigger angina pectoris in people who have CAD.

Alpha Blockers

Alpha blockers, also called alpha adrenergic antagonist medications, block alpha receptors in the cells from binding with EPINEPHRINE (also called adrenaline). These drugs were among the first generation of antihypertensive medications, though beta blockers and other antihypertensives have generally replaced them. Alpha blockers relax smooth MUSCLE, including that in the walls of the arteries to produce arterial dilation. This reduces the resistance for the flow of blood, lowering blood pressure. The most common cardiovascular use of alpha blockers is to treat hypertension that arises from PHEOCHROMOCYTOMA. This endocrine tumor secretes the hormones epinephrine and NOREPINEPHRINE, causing extreme spikes in blood pressure.

Alpha blockers are not a first-line treatment approach for general hypertension because their effects are widely systemic and because their long-term use increases the risk for heart failure. Alpha blockers affect other sites of smooth muscle tissue throughout the body, such as in the gastrointestinal tract, acting to slow peristalsis, and in the genitourinary system, causing URINARY INCONTINENCE and ERECTILE DYSFUNCTION. Other side effects may include dizziness and SYNCOPE (fainting). Some alpha blockers also block beta receptors.

COMMON ALPHA BLOCKERS

clonidine (Catapres)	doxazosin (Cardura)
guanabenz (Wytensin)	guanfacine (Tenex)
labetalol (Normodyne)	methyldopa (Aldomet)
phenoxybenzamine (Dibenzyline)	prazosin (Minipress)
terazosin (Hytrin)	

Angiotensin II Receptor Blockers (ARBs)

Angiotensin II receptor blockers, also called angiotensin II receptor antagonists or ARBs, prevent the enzyme angiotensin II from binding with cells the walls of the arteries. Angiotensin II is a powerful endogenous vasoconstrictor (substance the body makes to narrow the blood vessels) that raises blood pressure. Preventing its actions relaxes and dilates the arteries, reducing the resistance blood encounters flowing through them and lowering blood pressure.

Pregnant women should not take angiotensin II receptor blockers (ARBs) during the second and third trimesters of PREGNANCY, as these drugs may cause harm or death to the fetus.

ARBs may be the first-line choice to treat hypertension, depending on the person's overall health profile and other medications. ARBs do not cause the cough and other side effects that can be troublesome with ACE inhibitors, though they do put more strain on the kidneys. The most common side effect with ARBs is headache, especially with losartan. Other side effects, though uncommon, may include anxiety, fatigue, and gastrointestinal upset.

COMMON ANGIOTENSIN II RECEPTOR BLOCKERS

candesartan (Atacand)	eprosartan (Teveten)
irbesartan (Avapro)	losartan (Cozaar)
olmesartan medoxomil (Benicar)	tasosartan (Verdia)
telmisartan (Micardis)	valsartan (Diovan)

Anticoagulants

People commonly refer to anticoagulant drugs as "blood thinners" though this is somewhat of a misnomer. The first stage of clotting, which anticoagulants delay, is a thickening of the blood as CLOTTING FACTORS begin causing cells to stick together. Anticoagulants prevent the body from processing vitamin K, which interferes with the blood's ability to activate clotting factors. Heparin, low molecular weight heparin (LMWH), and fondaparinux are injectable anticoagulants that are relatively short-acting though have cumulative effects when administered for extended periods of time. Surgeons use anticoagulants to completely suppress the blood's clotting ability during operations that require CARDIOPULMONARY BYPASS. Warfarin (Coumadin) is currently the only oral anticoagulant available, though research continues to search for alternatives. Anticoagulants are NTI drugs that require continual monitoring to maintain therapeutic levels.

Women who are pregnant or planning to become pregnant should not take warfarin, as it can cause birth defects (highest risk during first trimester).

Doctors prescribe anticoagulant medications to prevent blood clots from forming, typically to prevent DEEP VEIN THROMBOSIS (DVT) and PULMONARY EMBOLISM in PERIPHERAL VASCULAR DISEASE (PVD) with INTERMITTENT CLAUDICATION, and to prevent heart attack and stroke. Anticoagulants cannot dissolve clots that already exist (though thrombolytic agents can). The most significant side effect is excessive bleeding. Anticoagulants can interact with numerous medications. Foods high in vitamin K (such as dark green leafy vegetables) may increase the blood's clotting capability.

COMMON ANTICOAGULANTS

heparin	fondaparinux (Arixtra)
warfarin (Coumadin)	
LMWHs:	
ardeparin (Normiflo)	dalteparin (Fragmin)
enoxaparin (Lovenox)	nadroparin (Fraxiparine)
reviparin (Clivarine)	tinzaparin (Innohep)

Antiplatelet Agents

Antiplatelet agents also interfere with the blood's ability to clot by blocking platelets, the cells that initiate clotting, from aggregating or sticking together. PLATELET AGGREGATION sets in motion the sequence of chemical interactions that activate clotting factors; blocking PLATELET aggregation

delays the start of the clotting process. Antiplatelet agents often are part of an ANTICOAGULATION THERAPY regimen, in combination with anticoagulant medications.

The most commonly used antiplatelet agent is low-dose aspirin, which health experts recommend for people who have increased risk for cardiovascular disease or who have already had heart attack or ischemic stroke. Like anticoagulants, antiplatelet agents require close monitoring to maintain therapeutic levels. Three antiplatelet agents are injectable only—abciximab (Rheopro), eptifibatide (Integrilin), and tirofiban (Aggrastat)—which doctors use during ANGIOPLASTY and sometimes other CARDIAC CATHETERIZATION procedures. The oral antiplatelet agent cilostazol (Pletal) also acts to dilate the blood vessels, so doctors often prescribe it to treat intermittent claudication.

Doctors typically prescribe antiplatelet agents to prevent clots from forming in people who have PVD, CAD, valvular heart disease, prosthetic heart valves, PACEMAKER or IMPLANTABLE CARDIOVERTER DEFIBRILLATOR (ICD), or who have had heart attack, stroke, or certain kinds of heart surgery. The most significant side effect of antiplatelet agents is excessive bleeding. Over-the-counter NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) such as ibuprofen, and the herbal product ginkgo biloba, also have mild antiplatelet activity; it is important to check with the doctor or pharmacist before taking them with prescribed antiplatelet agents.

COMMON ANTIPLATELET AGENTS

abciximab (Rheopro)	cilostazol (Pletal)
clopidogrel (Plavix)	dipyridamole (Persantine)
eptifibatide (Integrilin)	sulfinpyrazone (Anturane)
ticlopidine (Ticlid)	tirofiban (Aggrastat)

Beta Blockers

Beta blockers, also called beta adrenergic antagonist medications or class II antiarrhythmics, block beta receptors in the cells from binding with epinephrine. Beta receptors are specific to the arteries and MYOCARDIUM, so the actions of beta blockers are selective and specific to these sites. In the heart, beta blockers slow the conduction of electrical impulses, which slows the heart rate and reduces the amount of blood the heart pumps (CARDIAC OUTPUT). These effects result in lowered blood pressure and also reduced cardiac workload, which relieves angina pectoris. In the arteries, beta blockers cause smooth muscle tissue to relax, which dilates the arteries to decrease the resistance blood encounters to lower blood pressure. Most beta blocker medications thus do not have the systemic or generalized effects of alpha blockers, though a few of the beta blockers (notably propanolol and sotalol) also have some alpha antagonist activity as well and may have mild systemic effects.

There are two kinds of beta receptors, beta 1 and beta 2. Muscle cells in the myocardium and NERVE cells that regulate heart rate contain primarily beta 1 receptors. Peripheral arteries and arterioles contain primarily beta 2 receptors. Different beta blocker drugs target either beta 1 or beta 2 receptors. The smooth muscle cells in the airways also contain beta 2 receptors, so beta blockers that affect beta 2 receptors in the blood vessels also affect the airways. Medications to treat ASTHMA may interact with beta blockers taken to treat cardiovascular conditions. Beta blockers prescribed for other conditions such as asthma, BENIGN PROSTATIC HYPERTROPHY (BPH), migraine headaches, GLAUCOMA, and essential tremor may also affect cardiovascular function.

Do not suddenly stop taking a beta blocker, as doing so may cause intensified ANGINA PECTORIS and increased risk for HEART ATTACK.

Beta blockers are the "workhorse" drugs in cardiology, treating a broad spectrum of cardiovascular conditions. Doctors prescribe beta blockers to treat hypertension, heart failure (especially congestive heart failure), atrial fibrillation, mild to moderate ventricular tachycardia, CARDIOMYOPATHY, angina pectoris, and to improve survival following heart attack. The most common side effects are fatigue and sleepiness, which generally improve with taking the medication over time. Beta blockers may cause erectile dysfunction in men and diminished sexual response in women. CAFFEINE and antihistamines (such as in cold and allergy products) intensify, and ALCOHOL diminishes, the effects of beta blockers. Beta blockers may interfere with the actions of oral ANTIDIABETES MEDICATIONS.

COMMON BETA BLOCKERS

acebutolol (Sectral)	atenolol (Tenormin)
betaxolol (Kerlone)	bisoprolol (Zebeta)
carteolol (Cartrol)	esmolol (Brevibloc)
metoprolol (Lopressor, Toprol)	nadolol (Corgard)
penbutolol (Levatol)	pindolol (Visken)
propranolol (Inderal)	timolol (Blocadren)

Calcium Channel Blockers

Calcium channel blockers, also called calcium channel antagonists, limit the amount of calcium that enters contractile cells. Two of the commonly prescribed calcium channel blockers act nearly exclusively on the heart (myocardial cells), diltiazem and verapamil. Cardiologists prescribe these drugs, also identified as class IV antiarrhythmics, to treat atrial fibrillation, PAT, hypertrophic cardiomyopathy, and angina pectoris. The other calcium channel blockers, sometimes called dihydropyridine calcium channel blockers, act primarily on the peripheral arteries, causing them to relax and dilate. This lowers resistance for blood flow and reduces blood pressure. Cardiologists prescribe these calcium channel blockers to treat hypertension, angina pectoris without arrhythmia, and RAYNAUD'S SYNDROME. Doctors use nimodipine following stroke to reduce the risk of arterial spasm and resulting HEMORRHAGE, as it affects primarily the arteries in the BRAIN.

Women who are pregnant or planning to become pregnant should not take calcium channel blockers, as these drugs can cause serious birth defects and STILLBIRTH.

COMMON CALCIUM CHANNEL BLOCKERS

amlodipine (Norvasc, Lotrel)	diltiazem (Cardizem, Cartia, Dilacor, Diltia, Tiazac)
felodipine (plendil)	nicardipine (Cardene)
isradipine (DynaCirx)	nimodipine (Nimotop)
nifedipine (Adalat, Procardia)	nisoldipine (Sular)
verapamil (Calan, Covera, Isoptin, Verelan)	

Side effects that may occur when taking calcium channel blockers include headache, gastrointestinal upset, fatigue, and peripheral edema. Most side effects retreat after a few weeks of taking the medication. Grapefruit and grapefruit juice interfere with most calcium channel blockers, preventing them from working properly.

Diuretics

People commonly refer to diuretic medications as "water pills" because they draw extra fluid from the body, increasing urination. The purpose is to reduce the volume of blood, which lowers blood pressure. Diuretics also help prevent edema (fluid accumulations in body tissues) such as may occur with heart failure. Doctors often prescribe diuretics in combination with other medications. There are four classifications of diuretic medications, defined by the drug's mechanism of action: ALDOSTERONE blockers, loop diuretics, potassium-sparing diuretics, and thiazides.

Aldosterone blockers Aldosterone blockers act by restricting adrenal gland production of the HORMONE aldosterone, which increases the amount of sodium the KIDNEYS withdraw from the blood. They affect the RENIN-angiotensin-aldosterone (RAA) hormonal system, one of the body's primary blood pressure regulatory systems. Though aldosterone blockers prevent the kidneys from reabsorbing sodium, they decrease the loss of potassium so they are also designated as "potassium-sparing." However, new understanding emerged in the early 2000s about other effects aldosterone has on the heart, particularly following heart attack and in heart failure and with respect to the RAA hormonal system, that have caused doctors to view aldosterone blockers as a separate category of diuretic.

The two aldosterone blockers available in the United States are eplerenone (Inspra) and spironolactone (Aldactone).

Loop diuretics Loop diuretics act on a site within the glomerular structure of the kidney called the loop of Henle, which regulates sodium reabsorption. Loop diuretics cause the kidneys to pass more sodium, and consequentially more water, into the urine, and are the most potent of the diuretic drugs. As the loop of Henle also plays a role in potassium regulation, loop diuretics also decrease potassium reabsorption and can result in potassium depletion. Doctors may also prescribe potassium supplementation to offset this effect. The most common side effect of loop diuretics is

headache. Loop diuretics also can damage the structures of the inner EAR, resulting in temporary or permanent HEARING LOSS.

COMMON LOOP DIURETICS

bumetanide (Bumex)	ethacrynic acid (Edecrin)
furosemide (Lasix, Myrosemide)	torsemide (Demadex)

Potassium-sparing diuretics These drugs prevent the kidneys from withholding sodium, the electrolyte most responsible for fluid retention, though allow the kidneys to pull potassium from the blood. They are the least potent of the diuretic drugs, acting on other sites in the glomeruli that regulate specifically sodium reabsorption. The two potassium-sparing diuretics available in the United States are amiloride (Midamor) and triamterene (Dyrenium). The aldosterone blockers eplerenone and spironolactone are also potassium sparing.

Thiazide diuretics The thiazide diuretics are the first line of therapy for hypertension and heart failure, often in combination with other cardiovascular medications. Their actions are more moderate than those of the loop diuretics, creating less of a risk for potassium depletion though such risk still exists. There are numerous thiazide diuretics, only some of which doctors prescribe for cardiovascular conditions. Because thiazides are so commonly used with other medications, there are also numerous formulations that incorporate a thiazide with another cardiovascular drug.

COMMON THIAZIDE DIURETICS

chlorothiazide (Diuril, Diurigen)
chlorthalidone (Hygroton, Thalitone)
hydrochlorothiazide (Ezide, Esidrix, HCTZ, Hydro-Chlor, Hydro-D, HydroDIURIL, Microzide, Oretic)
hydroflumethiazide (Diucardin, Saluron)
methyclothiazide (Aquatensen, Enduron)
metolazone (Diulo, Mykrox, Zaroxolyn)
polythiazide (Renese)
quinethazone (Hydromox)
trichlormethiazide (Metahydrin, Naqua, Trichlorex)

Inotropics

Inotropic drugs draw more calcium into myocardial cells, intensifying their contractility (the force with which they contract) and increasing the heart's effectiveness while decreasing the effort required. Inotropic drugs administered intravenously during cardiovascular emergency include dopamine, dobutamine, and milrinone; these drugs give the heart a "jolt" to help it pull out of CARDIAC ARREST. Digoxin (short-acting) and digitoxin (long-acting), forms of digitalis, are the inotropic medications for chronic or extended oral therapy. Though once the cornerstone of therapy for heart failure (notably congestive heart failure), digoxin has a very narrow therapeutic index, making toxicity a worrisome concern. Digoxin interacts with numerous other medications including those that more effectively treat heart failure, and the heart becomes dependent on it.

Digoxin also acts to slow the number of electrical impulses that cross the ATRIOVENTRICULAR (AV) NODE, slowing and regulating the contractions of the myocardial cells. Cardiologists may prescribe digoxin to treat atrial fibrillation. The most common brand name digoxin product in the United States is Lanoxin.

Lipid-Lowering

Lipid-lowering medications reduce blood levels of cholesterol and triglycerides, lowering the risk for atherosclerosis and its related conditions CAD and PVD. There are four classifications of lipid-lowering medications, each with a different mechanism of action: BILE acid sequestrants, fibrates, statins, and selective cholesterol absorption inhibitors. As well, niacin acts to block cholesterol and lipoprotein synthesis in the LIVER.

Bile acid sequestrants The bile acid sequestrants were the first cholesterol-lowering medications to become available. They work by binding with bile in the gastrointestinal tract, preventing the body from reabsorbing cholesterol the bile contains. Bile acid sequestrants can reduce low-density lipoprotein cholesterol (LDL-C) by about 20 percent and total cholesterol by 5 to 10 percent. These medications come as powders to mix with juices or foods such as applesauce, and commonly cause gastrointestinal distress. Bile acid sequestrants interact with numerous medications, including beta blockers, diuretics, and the anticoagulant warfarin.

COMMON BILE ACID SEQUESTRANTS

cholestyramine (Questran, Prevalite)	colesevelam (WelChol)
	colestipol (Colestid)

Fibrates The fibrates work by blocking the liver's production of LDL and VLDL (very low-density lipoprotein), the carriers for triglycerides. However, fibrates do not lower LDL-C or VLDL-C in the blood. Rather, they primarily reduce triglycerides though also raise high-density lipoprotein cholesterol (HDL-C), the "good" cholesterol. The most common side effect of fibrates is gastrointestinal distress, which usually disappears after taking the medication for a few weeks.

COMMON FIBRATES

clofibrate (Atromid-S)	fenofibrate (Tricor)
gemfibrozil (Lopid)	

Statins Statins—or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors—are the most commonly prescribed lipid-lowering medications. They work by blocking the action of HMG-CoA reductase, an enzyme necessary for the liver to synthesize cholesterol. Statins can lower blood LDL cholesterol by as much as 35 percent in just three to six weeks, making them very effective at quickly lowering the risk for atherosclerosis-related cardiovascular events. Statins reduce the risk for the progression of CAD, which could improve heart function after heart attack and are part of the standard medication regimen after heart attack and HEART TRANSPLANTATION. Common side effects of statins include gastrointestinal distress, fatigue, headache, and sleep disturbances.

COMMON STATINS

atorvastatin (Lipitor)	fluvastatin (Lescol)
lovastatin (Mevacor)	pravastatin (Pravachol)
simvastatin (Zocor)	

Selective cholesterol absorption inhibitors The selective cholesterol absorption inhibitors block the gastrointestinal tract from absorbing dietary cholesterol, limiting the cholesterol that enters the bloodstream. Ezetimibe (Zetia) is currently the only drug in this classification that is available in the United States. Doctors often prescribe ezetimibe in combination with statin medications for the most effective lipid-lowering effect.

Potassium Channel Blockers

Potassium channel blockers, also called potassium channel antagonists or class III antiarrhythmics, limit the amount of potassium, a key electrolyte (chemical that can carry an electrical impulse), that can enter myocardial cells. This limitation restricts the flow and pattern of electrical impulses through the heart in very specific ways. Cardiologists prescribe potassium channel blockers to treat atrial fibrillation that does not respond to other medications and to treat atrial tachycardia. These drugs interact with numerous medications, including those prescribed to treat cardiovascular conditions (notably digoxin and warfarin) and to treat other health conditions such as DIABETES. Amiodarone increases sensitivity to ultraviolet light, which can result in severe SUNBURN even through clothing. Potassium channel blockers have numerous serious side effects including life-threatening or fatal arrhythmias and TORSADE DE POINTES, a highly unstable form of ventricular tachycardia.

COMMON POTASSIUM CHANNEL BLOCKERS

amiodarone (Cordarone)	dofetilide (Tikosyn)
ibutilide (Corvert)	

Sodium Channel Blockers

Sodium channel blockers, also called sodium channel antagonists or class I antiarrhythmics, limit the amount of sodium that enters myocardial cells. This limitation restricts the flow and pattern of electrical impulses through the heart in very specific ways that differ from the actions of potassium channel blockers. Because sodium is critical for myocardial contraction, restricting it requires a delicate therapeutic balance. Cardiologists reserve sodium channel blockers to treat potentially life-threatening ventricular tachycardia that does not respond to other treatment. The risks and complications of these medications are numerous and serious; they can cause fatal arrhythmias.

COMMON SODIUM CHANNEL BLOCKERS

disopyramide (Norpace)	flecainide (Tambocor)
mexiletine (Mexitil)	moricizine (Ethmozine)
procainamide (Pronestyl)	propafenone (Rythmol)
quinidine (Cardioquin, Quinidex)	

Thrombolytic Agents

Thrombolytic agents, commonly called "clot busters," dissolve blood clots that have already formed. Given early enough, they can prevent the

clot from forming, essentially halting heart attack or stroke before the event can cause any damage. However, doctors must administer them within three to four hours of clot formation. After four hours the clot has hardened and thrombolytic agents cannot dissolve them.

Thrombolytic agents are substances, either natural extracts or recombinant forms, that convert plasminogen in the blood to plasmin, an enzyme that dissolves fibrin. Fibrin is the substance in the blood that forms the webbing of the clot structure to snare platelets and other substances in the blood that become the clot. Early in the COAGULATION process fibrin is a semisolid, stringlike substance similar to the strands of a spiderweb. As the coagulation process continues, however, the fibrin strands and the cellular matter they have captured harden into the solid structure of a blood clot. Once the fibrin hardens, plasmin has no effect on it.

The most frequently used thrombolytic agents are tissue plasminogen activators (tPAs). One of the original thrombolytic agents, streptokinase, derives from the streptococcus bacterium and causes the body to develop antibodies against it. Because of this, doctors cannot administer streptokinase if the person has received streptokinase within 12 months. However, it takes about five days for the body to produce antibodies, allowing multiple administrations within five days of the initial dose. The tPAs do not seem to have this limitation, although it is possible for the body to develop antibodies against them as well.

Doctors administer thrombolytic agents intravenously to treat heart attack, stroke, deep vein thrombosis, and pulmonary embolism. The effect is rapid and short acting. Excessive and severe bleeding is a significant risk, particularly when stroke is hemorrhagic rather than ischemic. Doctors make every effort to determine the nature of a stroke before administering thrombolytic agents, though sometimes bleeding occurs even with ischemic stroke. As well, these agents may disturb the integrity of clots that have formed within the previous 10 days, such as from surgery.

COMMON THROMBOLYTIC AGENTS

alteplase (Activase)	anistreplase (Eminase)
reteplase (Retavase)	streptokinase (Streptase, Kabinase)
tenecteplase (TNKase)	urokinase (Abbokinase)

Vasoconstrictors

Vasoconstrictors cause the blood vessels to constrict, or tighten, to raise blood pressure. Doctors administer vasoconstrictors to treat cardiovascular SHOCK and HYPOTENSION. Many bronchodilating medications prescribed to treat asthma also have peripheral vasoconstriction action, and may raise blood pressure at the same time they open the airways. One of the most commonly used vasoconstrictors is pseudoephedrine, found in cold, flu, and some allergy medications. Caffeine and NICOTINE are also vasoconstrictors. Though doctors do not prescribe these products for cardiovascular use, they have the effect of raising blood pressure as well as increasing heart rate. The most commonly used vasoconstrictor for cardiovascular purposes is midodrine (ProAmatine).

Vasodilators

Many medications to treat hypertension are vasodilators, drugs that cause the blood vessels to relax so more blood can flow through them with less resistance. These medications may lower blood pressure or relieve angina pectoris. Among the general vasodilators cardiologists might prescribe to treat hypertension are hydralazine and minoxidil. Both drugs regulate the calcium that enters the smooth muscle cells of the ARTERY walls, slowing their contractility and causing the arteries to relax (dilate). Minoxidil is an NTI drug that requires close monitoring because, although it is a potent peripheral vasodilator, it also increases heart rate and has other cardiovascular actions that require additional medications to moderate.

Nitrate vasodilators are especially effective at relaxing the coronary arteries to relieve angina pectoris, which is one of the leading reasons doctors prescribe them. Nitrates also dilate the peripheral veins, which decreases the heart's workload. Nitrates come in sublingual tablets placed under the tongue at the onset of anginal symptoms, regular and long-acting oral medications, transdermal (skin) patches, and topical ointments. Because the body acquires a tolerance to nitrates, dosing schedules are particularly important. Other commonly prescribed medications that have vasodilating actions include certain of the beta blockers, calcium channel blockers, ACE inhibitors, and ARBs.

COMMON VASODILATORS

hydralazine (Apresoline)
mecamylamine (Inversine)
minoxidil (Loniten)

Nitrates

isosorbide dinitrate (Isordil, Sorbitrate)
isosorbide mononitrate (Imdur, ISMO, Monoket)
nitroglycerin (Nitro-Dur, Nitrolingual, Nitrostat)

See also ADRENAL GLANDS; ANTIBODY; BACTERIA; LIVING WITH CARDIOVASCULAR DISEASE.

microinfarction Tiny arterial occlusions that briefly block the flow of BLOOD to the BRAIN, causing transient ischemic attacks (TIAs), or to the HEART. What microinfarction lacks in initial effect it makes up through frequency. Microinfarction may also affect other key organs such as the KIDNEYS and LIVER. Conditions that can result in microinfarction include severe ATHEROSCLEROSIS, PERIPHERAL VASCULAR DISEASE (PVD), CORONARY ARTERY DISEASE (CAD), INTERMITTENT CLAUDICATION, and DEEP VEIN THROMBOSIS (DVT). Microinfarction also may

MEDICATIONS TO TREAT CARDIOVASCULAR CONDITIONS

Type of Medication	Common Products	Actions/Effects	Cardiovascular Conditions
ACE inhibitor	benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril	dilate peripheral arteries and arterioles; lower BLOOD PRESSURE	HEART FAILURE; HYPERTENSION; VALVULAR HEART DISEASE; used after HEART ATTACK to prevent subsequent heart attack
adenosine (intravenous hospital administration only)	adenosine	slow the HEART RATE	PAROXYSMAL ATRIAL TACHYCARDIA (PAT); WOLFF-PARKINSON-WHITE SYNDROME
alpha blocker	clonidine, doxazosin, guanabenz, guanfacine, labetalol, mecamylamine, methyldopa, phenoxybenzamine, prazosin, terazosin	block the actions of EPINEPHRINE and NOREPINEPHRINE on the HEART and arteries; dilate peripheral blood vessels; lower blood pressure	hypertension
angiotensin II receptor blocker	candesartan, eprosartan, irbesartan, losartan, telmisartan, valsartan	dilate peripheral arteries and arterioles; lower blood pressure	heart failure; hypertension
anticoagulant	dalteparin, enoxaparin, heparin, tinzaparin, warfarin	inhibit activation of CLOTTING FACTORS; reduce blood's ability to clot	ATRIAL FIBRILLATION; DEEP VEIN THROMBOSIS; heart attack prophylaxis; INTERMITTENT CLAUDICATION; STROKE prophylaxis; PERIPHERAL VASCULAR DISEASE; PULMONARY EMBOLISM
antiplatelet	aspirin, cilostazol, clopidogrel, dipyridamole, fondaparinux, ginkgo biloba, sulfinpyrazone, ticlopidine	inhibit PLATELET AGGREGATION; reduce blood's ability to clot	ANGINA PECTORIS; deep vein thrombosis; heart attack prophylaxis; intermittent claudication; stroke prophylaxis; STENT placement

Type of Medication	Common Products	Actions/Effects	Cardiovascular Conditions
beta blocker	acebutolol, atenolol, betaxolol, bisoprolol, carteolol, carvedilol, esmolol, labetalol, metoprolol, nadolol, penbutolol, pindolol, propranolol, sotalol, timolol	block the actions of epinephrine and norepinephrine on the heart and arteries; dilate the arteries; slow the heart rate; lower blood pressure	angina pectoris; atrial fibrillation; CARDIOMYOPATHY; heart failure; hypertension; PALPITATIONS; used after heart attack to prevent subsequent attack
calcium channel blocker	amlodipine, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, verapamil	dilate arteries; relax myocardial cells; slow heart rate; lower blood pressure	angina pectoris; atrial fibrillation; cardiomyopathy; heart failure; hypertension
diuretic	amiloride, bumetanide, chlorthalidone, chlorothiazide, eplerenone, ethacrynic acid, furosemide, hydrochlorothiazide, indapamide, metolazone, polythiazide, spironolactone, torsemide, triamterene	reduce excess fluid; lower blood pressure; reduce heart's workload	edema; heart failure; hypertension
inotropic	digoxin, digitoxin	strengthen heart MUSCLE; slow heart rate in atrial fibrillation; reduce heart's workload	atrial arrhythmias; heart failure
lipid-lowering	atorvastatin, bezafibrate, cholestyramine, clofibrate, colesevelam, colestipol, ezetimibe, fenofibrate, fluvastatin, gemfibrozil, pitavastatin, lovastatin, rosuvastatin, simvastatin, niacin	limit lipid synthesis or absorption; lower cholesterol and triglyceride blood levels	HYPERLIPIDEMIA; statins after heart attack
nitrate	erythrityl tetranitrate, isosorbide dinitrate, isosorbide mononitrate, nitroglycerin, pentaerythritol tetranitrate	dilate arteries in the heart to increase blood flow to the heart; dilate veins in the body to decrease the heart's workload	angina pectoris
potassium channel blocker	amiodarone, dofetilide, ibutilide	regulate heart rate	atrial fibrillation; atrial tachycardia

Type of Medication	Common Products	Actions/Effects	Cardiovascular Conditions
sodium channel blocker	disopyramide, flecainide, mexiletine, moricizine, procainamide, propafenone, quinidine, tocainide	slow electrical conduction in the heart; regulate heart rate	severe ventricular tachycardia
thrombolytic (intravenous hospital administration only)	anistreplase, streptokinase, tissue plasminogen activator (tPA), urokinase	dissolve blood clots	deep vein thrombosis; ischemic stroke; MYOCARDIAL INFARCTION
vasoconstrictor	epinephrine	constrict blood vessels; raise blood pressure	HYPOTENSION
vasodilator	hydralazine, isosorbide dinitrate, isosorbide mononitrate, mecamylamine, minoxidil, nitroglycerin	dilate blood vessels; decrease the heart's workload; lower blood pressure	angina pectoris; CORONARY ARTERY DISEASE; hypertension

occur after surgical operations or major trauma, when clot fragments break away from HEALING wounds. Doctors use ANTICOAGULATION THERAPY to control microinfarction.

See also ASPIRIN THERAPY; HEART ATTACK; ISCHEMIC HEART DISEASE; KIDNEY; MYOCARDIAL INFARCTION; STROKE; TRANSIENT ISCHEMIC ATTACK (TIA).

minimally invasive cardiac surgery Surgical methods that combine ENDOSCOPY and CARDIAC CATHETERIZATION to repair damaged HEART valves or clear obstructive ATHEROSCLEROTIC PLAQUE. Some methods involve making several small incisions in the chest and between the ribs to gain access to the heart. Others involve inserting microscopic tools, via cardiac catheterization, into the heart. There remain questions as to whether minimally invasive cardiac surgery is of greater or lesser risk than OPEN HEART SURGERY.

Though significantly less traumatic, minimally invasive cardiac surgery restricts the surgeon's ability to see the condition of the heart. Minimally invasive cardiac surgery done "off-pump" (without CARDIOPULMONARY BYPASS), further challenges the surgeon's ability to operate on a moving target. Countering these concerns are the reduced trauma to the chest because the STERNUM (breastbone) can remain intact, as well as avoiding the risks of cardiopulmonary bypass. Recovery is much more rapid and significantly less painful than with traditional open heart surgery. However, the surgeon cannot reach the back of the heart using minimally invasive procedures, limiting the value of these methods for treating CORONARY ARTERY DISEASE (CAD) that involves the posterior CORONARY ARTERIES.

See also MINIMALLY INVASIVE SURGERY; POSTOPERATIVE PROCEDURES; PREOPERATIVE PROCEDURES; SURGERY BENEFIT AND RISK ASSESSMENT.

myocardial infarction Death of HEART tissue. The most common cause of myocardial infarction is occlusion of the CORONARY ARTERIES such as occurs as a consequence of CORONARY ARTERY DISEASE (CAD) or less frequently of coronary ARTERY spasm. Myocardial infarction is the clinical term doctors use for HEART ATTACK. The MYOCARDIUM has very high oxygen needs, as oxygen is the only energy source for myocardial cells (unlike most other cells in the body, except the BRAIN, that also use GLUCOSE for energy). Myocardial tissue does not have significant ability to regenerate.

Myocardial tissue that dies not only can no longer contract to aid in the heart's function but

also cannot conduct electrical impulses to reach undamaged tissue. Myocardial infarction results in "dead" areas of the heart MUSCLE that cannot participate in the CARDIAC CYCLE, which often results in ARRHYTHMIA as well as ineffective pumping ability. The cellular structure of these areas changes, initially becoming soft and subsequently becoming fibrous (scarlike). New arteries are often able to develop, through a process called angiogenesis, to carry BLOOD around infarcted areas of the heart. This helps the rest of the heart remain functional. However, large infarctions may overcome the heart, resulting in heart attack or CARDIAC ARREST.

ELECTROCARDIOGRAM (ECG) and ECHOCARDIOGRAM are the diagnostic procedures that typically identify myocardial infarction. Treatment includes eliminating the cause of the infarction, such as coronary artery occlusion, and stabilizing the heart's function to the best extent possible with medications. Because CAD is nearly always the culprit, ANGIOPLASTY or CORONARY ARTERY BYPASS GRAFT (CABG) are nearly always among the treatment options.

See also CARDIOVASCULAR DISEASE PREVENTION; MEDICATIONS TO TREAT CARDIOVASCULAR DISEASE; MICROINFARCTION; MYOCARDIAL PERFUSION IMAGING; STROKE; SURGERY BENEFIT AND RISK ASSESSMENT; TRANSIENT ISCHEMIC ATTACK (TIA).

myocardial perfusion imaging A radionuclide procedure that allows cardiologists to observe the flow of BLOOD from the CORONARY ARTERIES into the tissues of the MYOCARDIUM (HEART MUSCLE). The test usually involves a resting and an exercise component, to provide a comprehensive picture of how much blood the heart receives to assess the extent to which CORONARY ARTERY DISEASE (CAD) is reducing cardiac function. The procedure takes about an hour and requires little preparation (namely, abstaining from STIMULANTS such as CAFFEINE and NICOTINE for 48 hours before the procedure).

The cardiologist administers a small amount of a radioactive substance, called a radionuclide or radioisotope (most commonly thallium), into a VEIN in the back of the hand or in the arm. The radionuclide is mixed in a solution, usually GLUCOSE, that the blood carries to the cells. The radionuclide rides along as a "tag" on the glucose molecules, accompanying them into the cells. The radionuclide rapidly disintegrates, releasing a pattern of electromagnetic energy called gamma-rays. A special device called a gamma camera detects the gamma rays, and presents them as images. The concentrations of energy tell cardiologists where myocardial blood flow is strong and where it is restricted, helping identify areas of ischemia (oxygen-deprived tissue).

When actual physical exercise is not feasible, the cardiologist may use a DRUG (often dipyridamole) to chemically simulate the effects of exercise on the heart. People who have ANGINA PECTORIS or significant CAD may feel temporary discomfort during this simulation. There are no side effects from myocardial perfusion imaging. The radionuclides cardiologists use emit minimal radioactivity and are gone from the body within a few hours.

See also COMPUTED TOMOGRAPHY (CT) SCAN; ECHOCARDIOGRAM; MAGNETIC RESONANCE IMAGING (MRI); POSITRON EMISSION TOMOGRAPHY (PET) SCAN; SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT) SCAN.

myocarditis INFLAMMATION of the HEART MUSCLE, often as a consequence of viral INFECTION that originates elsewhere in the body (such as a cold). Viruses known to cause myocarditis include MEASLES, RUBELLA, coxsackie, and CYTOMEGALOVIRUS (CMV). Myocarditis also may be bacterial, or the consequence of cardiotoxic exposure (such as to radiation or carbon monoxide). The autoimmune processes of systemic inflammatory disorders such as SYSTEMIC LUPUS ERYTHEMATOSUS (SLE), SARCOIDOSIS, and RHEUMATOID ARTHRITIS also can involve the myocardium. A rare and severe form of myocarditis is giant cell myocarditis, an autoimmune disorder that specifically attacks the heart.

Myocarditis may have few symptoms until there is significant damage to the heart (commonly in the form of CARDIOMYOPATHY and ARRHYTHMIA), and often is life-threatening. Symptoms of early or chronic myocarditis may mimic those of INFLUENZA or of HEART ATTACK. Diagnosis is by myocardial biopsy performed via CARDIAC CATHETERIZATION, which reveals the infiltration of lymphatic cells and other characteristic changes in the myocardium that identify an inflammatory process. Chronic or advanced myocarditis may

have FIBROSIS (scar tissue). Treatment targets relieving arrhythmias and HEART FAILURE, and may include IMMUNOSUPPRESSIVE THERAPY. HEART TRANSPLANTATION may become an option for end-stage heart failure.

See also AUTOIMMUNE DISORDERS; BACTERIA; COLDS; ENDOCARDITIS; PERICARDITIS; VIRUS.

myocardium The MUSCLE tissue that forms the walls of the HEART. Myocardial cells are unique in their structure, blending muscle and NERVE structures so they can both contract and conduct electrical impulses. Myocardial cells thus can contract independent of external stimulation. The myocardial fibers of the atria have a different configuration from those of the ventricles. The CORONARY ARTERIES provide an extensive network to supply blood to the myocardium, which requires about 70 percent of the blood's oxygen. With increasing age, fibrous and fatty tissue tends to infiltrate the myocardium, somewhat reducing its effectiveness.

CONDITIONS THAT CAN AFFECT THE MYOCARDIUM

CARDIOMYOPATHY	CONGENITAL ANOMALY
ISCHEMIC HEART DISEASE	MICROINFARCTION
MYOCARDIAL INFARCTION	MYOCARDITIS

CORONARY ARTERY DISEASE (CAD) is the most significant threat to the myocardium, as occlusions in the coronary arteries deprive the myocardium of blood and thus oxygen. When the consequence is MYOCARDIAL INFARCTION, CARDIAC ARREST can result.

For further discussion of the myocardium within the context of cardiovascular structure and function, please see the overview section "The Cardiovascular System."

See also ENDOCARDIUM; HEART FAILURE; PERICARDIUM.

myxoma A nonmalignant tumor that grows in the HEART, nearly always in one of the atria and most commonly in the left atrium. Myxoma arises from the ENDOCARDIUM and may be either firm or soft in consistency. The tumor can block the flow of BLOOD through the atrium, interfere with the function of the heart valves, or break apart to send fragments into the blood circulation that cause embolism (sudden blockage of an ARTERY) elsewhere in the body. Soft myxomas are more likely to fragment; firm myxomas are more likely to be occlusive. As a myxoma grows it causes increasing turbulence in the blood as it flows through the chamber, presenting a significant risk for the formation of blood clots. ECHOCARDIOGRAM generally provides definitive diagnosis. Treatment is OPEN HEART SURGERY to remove the tumor. Once removed, the tumor results in no residual consequences. Myxoma is most common in people between the ages of 30 years and 60 years.

See also ATRIAL FIBRILLATION; TRANSIENT ISCHEMIC ATTACK.

obesity and cardiovascular disease OBESITY, a condition in which excess body weight is 20 percent or more above healthy weight as a result of excessive body fat, emerged in the 1990s as an independent risk factor for CARDIOVASCULAR DISEASE (CVD). This means that without any other additional RISK FACTORS FOR CARDIOVASCULAR DISEASE, obesity makes CVD more likely. However, the relationship between obesity and CVD is complex. Other health conditions associated with obesity also increase the risk for numerous types of cardiovascular disease. Prominent among them are HYPERTENSION (high BLOOD PRESSURE), INSULIN RESISTANCE, HYPERLIPIDEMIA, and DIABETES. Some health experts believe obesity is as significant a risk factor for cardiovascular disease as cigarette smoking.

Doctors define obesity as a BODY MASS INDEX (BMI) of 30 kilograms per meter squared (kg/m^2) or higher. This corresponds to about 20 percent above healthy weight. BMI correlates body weight with health risk. At a BMI of 30, a person is likely to have at least one health condition associated with obesity. As BMI rises, so do the associated health conditions and the risk for cardiovascular disease. When BMI reaches 40, it is unusual for there *not* to be some form of cardiovascular disease present.

Obesity affects cardiovascular function mechanically and metabolically. Excessive body fat pressures the BLOOD vessels, causing the heart to work harder to pump blood through them. As well, there is more surface area that the cardiovascular

BMI AND CARDIOVASCULAR DISEASE RISK

BMI (kg/m2)	Cardiovascular Risk	Conditions
18.5–24.9: healthy	not affected	none
25–29.9: overweight	increased	HYPERLIPIDEMIA; HYPERTENSION manageable through lifestyle
30–34.9: OBESITY	high	hyperlipidemia; hypertension; ATHEROSCLEROSIS manageable through lifestyle and medication
35–39.9: severe obesity	very high	hyperlipidemia; hypertension; atherosclerosis; mild to moderate CORONARY ARTERY DISEASE (CAD); DIABETES (type 2); OBSTRUCTIVE sleep apnea management requires multiple medications
40+: morbid obesity	extremely high	hyperlipidemia; hypertension; atherosclerosis; moderate to severe CAD; symptomatic HEART FAILURE; diabetes; obstructive sleep apnea multiple medications necessary though may not entirely manage cardiovascular conditions

system must perfuse with blood. Excessive body fat may compress the neck, causing OBSTRUCTIVE SLEEP APNEA (episodes during sleep in which the person stops BREATHING). Obstructive sleep apnea prevents adequate air flow to the LUNGS, reducing oxygenation of the blood and causing ischemic episodes in which the heart does not receive enough oxygen, which results in ARRHYTHMIA. Excessive body fat may also compress the heart itself, further increasing the forces against which it must work to pump blood. All of these factors conspire to raise blood pressure and increase HEART RATE in an attempt to help the heart, which, if allowed to progress unchecked, are likely to result in HEART FAILURE.

Metabolically, obesity triggers INSULIN dysfunction. Because insulin plays a key role in cholesterol synthesis in the LIVER, hyperlipidemia is likely. Hyperlipidemia contributes to CORONARY ARTERY DISEASE (CAD) and PERIPHERAL VASCULAR DISEASE (PVD). A more significant health concern is the evolution from insulin resistance to diabetes. Diabetes increases cardiovascular disease risk substantially, as it is itself an independent risk factor for, as well as a leading cause of, cardiovascular disease.

When obesity declines even modestly, cardiovascular risk drops and cardiovascular health improves. As little as a 10-pound weight loss can drop systolic blood pressure by 10 millimeters of mercury (mm Hg). With sustained weight loss, many cardiovascular symptoms retreat and risk continues to fall.

See also BODY FAT PERCENTAGE; CARDIOVASCULAR DISEASE PREVENTION; EATING HABITS; DIET AND HEALTH; EXERCISE AND HEALTH; LIFESTYLE AND CARDIOVASCULAR HEALTH; OBESITY AND DIABETES; WEIGHT LOSS AND WEIGHT MANAGEMENT.

omega fatty acids and cardiovascular health Omega fatty acids are dietary substances that increase high-density lipoprotein cholesterol (HDL-C) and decrease low-density lipoprotein cholesterol (LDL-C). Omega fatty acids also reduce the likelihood of ARRHYTHMIA and may help lower BLOOD PRESSURE. The omega fatty acids that appear most beneficial are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Researchers do not know how omega fatty acids affect cardiovascular health though believe they reduce INFLAMMATION and the blood's clotting tendencies. These effects slow ATHEROSCLEROTIC PLAQUE accumulation and infiltration into the arterial intima, the innermost layer of the arterial wall.

The most abundant dietary sources of omega fatty acids are cold-water fish such as mackerel, tuna, and salmon. Health experts recommend eating at least two servings a week of these fish, which contain high levels of EPA and DHA, or taking supplements that provide 1 to 1.5 grams of EPA and DHA. People who have high levels of triglycerides may need to take higher doses. However, doses higher than 3 grams may cause excessive bleeding. Flaxseed and flaxseed oil, canola oil, soybeans and soybean foods such as tofu, and walnuts are good dietary sources of alpha-linolenic acid (LNA), from which the body can metabolize omega fatty acids.

An unresolved concern remains that of mercury contamination in cold-water fish. Mercury poisoning is particularly harmful to a developing FETUS and raises the risk for certain kinds of CANCER in adults. The US Environmental Protection Agency (EPA) routinely samples and reports mercury levels in different species of fish and issues advisories for those that exceed established safety levels. People who are concerned about mercury contamination can obtain omega fatty acids through dietary supplements, which appear equally effective.

See also CARDIOVASCULAR DISEASE PREVENTION; DIET AND CARDIOVASCULAR HEALTH; DIET AND HEALTH; NUTRITIONAL NEEDS; NUTRITIONAL SUPPLEMENTS.

open heart surgery Any OPERATION in which the surgeon opens the chest to expose the HEART. Open heart surgery is the most common method for CORONARY ARTERY BYPASS GRAFT (CABG), valvuloplasty and heart valve replacement, reconstructive operations to correct congenital heart malformations, and HEART TRANSPLANTATION. In the United States, surgeons perform about 750,000 open heart surgery operations each year, about 600,000 of which are CABG. Open heart surgery requires general ANESTHESIA and a hospital stay of 3 to 10 days, depending on the operation. Though most open heart operations also employ CARDIOPULMONARY BYPASS, in which a machine takes over the role of oxygenating and pumping the BLOOD so the

surgeon can operate on a still heart, there is a growing trend toward "off pump" operations that do not use cardiopulmonary bypass.

Surgical Procedure

For open heart surgery, the surgeon makes a long incision lengthwise along the top of the sternum (breastbone) through the SKIN and tissues beneath, and then makes a similar saw-cut through the sternum to enter the chest cavity. Special retractors spread the sternum and hold the incision open. To reach the heart, the surgeon must open the PERICARDIUM, the protective membranous sac that surrounds the heart. Often the surgeon leaves the pericardium open after the operation on the heart, to shorten surgery time and reduce the risk for postoperative complications.

For operations using cardiopulmonary bypass, the surgeon attaches the heart's major vessels to large tubes called cannulas, then clamps the heart vessels closed. The blood reroutes through the bypass machine. The surgeon can then bathe the heart in a cold concentrated potassium solution, which causes the heart to stop beating (cardioplegia). After completing the operation the surgeon reverses the process to restore circulation through the heart, closes the sternum with sturdy wire sutures and the skin with nylon sutures or staples. The SCAR that remains after the surgical wound heals remains fairly prominent for two to three years, after which it fades to a thin line.

When the operation is "off pump," the surgical team lowers the person's body temperature to slow body functions including heart contractions. The surgeon operates on the moving heart, which requires precise technique and timing. Inadvertent damage to the heart is a significant risk.

Risks and Complications

Many of the risks of open heart surgery are the same regardless of the operation. Key among them are

- excessive bleeding due to anticoagulants
- air embolism during cardiopulmonary bypass, which can cause STROKE
- difficulty restoring the heart to normal rhythm
- failure of the surgical procedure
- surgeon error
- unexpected anatomic anomalies

General complications that can occur after surgery include

- bleeding at the operative site or at the surface surgical wound
- INFECTION, either affecting the heart or the surgical wound
- blood clots, which may cause PULMONARY EMBOLISM, HEART ATTACK, or stroke
- ARRHYTHMIA
- HYPERTENSION and HEART FAILURE

Surgeons and the health-care team are alert for complications that can arise. Most people stay for 12 to 48 hours in a specialized cardiac surgery intensive care unit, where staff monitor cardiopulmonary function continuously. Many potential postoperative complications become less likely by 48 hours from surgery, though many people stay in the hospital for up to 10 days until the surgeon is confident that HEALING is well under way.

Outlook and Lifestyle Modifications

The outlook following open heart surgery depends to great extent on the reason the surgery was necessary. Many people return to normal activities after they recover from their operations, though may require frequent follow-up visits or medications. This is especially true for heart transplant recipients. The likelihood of complications diminishes as time passes and healing becomes complete.

Most people need to make some lifestyle changes after open heart surgery, typically in eating and exercise habits. Cardiologists recommend a diet that is nutritiously balanced and daily exercise such as walking. CARDIAC REHABILITATION programs help people get started with such changes, providing customized plans to accommodate the person's starting point as well as recovery goals.

See also LIFESTYLE AND CARDIOVASCULAR HEALTH; LIVING WITH CARDIOVASCULAR DISEASE; POSTOPERATIVE PROCEDURES; PREOPERATIVE PROCEDURES; SURGERY BENEFIT AND RISK ASSESSMENT.

Ornish program An intensive lifestyle-oriented method for reducing the risk for CORONARY ARTERY

DISEASE (CAD) and HEART ATTACK. Named for Dean Ornish, the American physician who developed the approach, the Ornish program features a strict vegetarian diet very low in fat along with daily YOGA, walking, MEDITATION, and participation in SUPPORT GROUPS. In the early 2000s in the United States, Medicare approved the Ornish program as an alternative treatment approach for CAD and rehabilitation following heart attack. The program arises from 25 years of clinical research supporting the effectiveness of restrictive diet to halt and sometimes reverse CAD. Numerous cardiovascular rehabilitation centers around the country offer the Ornish program. It is important to maintain the lifestyle changes after completing the structured program.

See also CARDIOVASCULAR DISEASE PREVENTION; LIFESTYLE AND CARDIOVASCULAR HEALTH.

P

pacemaker A small, implanted electronic device that emits electrical impulses to maintain a regular HEART RATE. The most frequent use of a pacemaker is to treat bradycardia, an ARRHYTHMIA in which the HEART rate is persistently below 60 beats per minute. A pacemaker may also be an effective treatment for obstructive CARDIOMYOPATHY, in which thickening of the heart wall interferes with the ability of the myocardial cells to convey electrical impulses.

Implanting the Pacemaker

The cardiologist implants the pacemaker during a brief procedure, with local anesthetic and a mild sedative to make the person comfortable. A standard pacemaker has two components: the pacing lead and the computerized control unit. The pacing lead extends through a BLOOD vessel into the heart, where the cardiologist positions it against the wall of the heart, usually the right ventricle or the right atrium. Some pacemakers may have two pacing leads, with one going into the right atrium and the other to the right ventricle.

The cardiologist then makes a small incision just below the collarbone to create a pocket that holds the control unit, and connects the pacing lead to the control unit. The cardiologist then programs the control unit to deliver an electrical impulse, a very mild electrical shock, when the heart rate falls below a specific threshold. Most pacemakers are set to respond "on demand," which means they emit pacing impulses only when the heart fails to generate them itself. The incision over the pacemaker control unit heals in about two or three weeks, leaving a barely noticeable protrusion.

Living with a Pacemaker

Some people notice when the pacemaker releases an electrical impulse, though most people are not aware. The "on demand" feature of current pacemakers allows the heart to accelerate its rhythm during physical exercise, sexual activity, and other situations in which the heart would naturally beat faster. Certain medical and dental equipment, such as MAGNETIC RESONANCE IMAGING (MRI), machines that deliver RADIATION THERAPY, and some dental drills also can interfere with pacemakers. Though earlier models of pacemakers were sensitive to electromagnetic interference from household appliances and other electronic devices, this is no longer the case. Only high-power devices such as welding equipment or power tools emit enough electromagnetic energy to disrupt a pacemaker. There is some question about the potential of interference from cellular and portable telephones. To be safe, cardiologists recommend keeping the phone at least six inches from, and holding it to the ear opposite, the pacemaker's control unit. Pacemakers run on lithium batteries and can function for about seven years before they need to be replaced.

See also CARDIAC RESYNCHRONIZATION THERAPY (CRT); IMPLANTABLE CARDIOVERTER DEFIBRILLATOR (ICD); MEDICATIONS TO TREAT CARDIOVASCULAR DISEASE; RADIOFREQUENCY ABLATION.

palpitations Perception that the HEART is racing, pounding, or skipping beats. Palpitations are may represent signs of underlying cardiovascular conditions such as ARRHYTHMIA though frequently signal high stress, anxiety, or excessive consumption of STIMULANTS such as CAFFEINE or NICOTINE (via cigarette smoking). When palpitations do suggest arrhythmia, they tend to occur along with other symptoms such as weakness and SYNCOPE (fainting). Awareness of the heartbeat is common during or immediately following strenuous exercise,

when the heart feels as if it were pounding, and right before falling asleep at night.

SUBSTANCES THAT CAN CAUSE PALPITATIONS	
albuterol	ALCOHOL
CAFFEINE	COCAINE
levothyroxine	ma huang
NICOTINE (tobacco)	pseudoephedrine
theophylline	

The most common presentation of palpitations is the premature beat, which can be atrial or ventricular and feels like a skipped beat though it is not. Because the premature beat is early, there is a slight pause before the regular beat which makes the regular beat feel enhanced. Such palpitations are nearly always the result of stimulants (including cold and flu preparations) or anxiety, and go away either when the stopping the stimulant or removing the cause of stress.

Palpitations require a doctor's evaluation when they occur

- frequently or for sustained periods of time
- with syncope or lightheadedness
- with chest discomfort
- with shortness of breath (DYSPNEA)
- in people who have diagnosed forms of CARDIOVASCULAR DISEASE (CVD) such as HYPERTENSION, CORONARY ARTERY DISEASE (CAD), and arrhythmia disorders

The arrhythmia disorders most likely to include palpitations among their symptoms are ATRIAL FIBRILLATION and PAROXYSMAL ATRIAL TACHYCARDIA (PAT), also called paroxysmal supraventricular tachycardia (PSVT). These disorders typically cause periods of rapid heartbeat. Though disconcerting, these arrhythmias are rarely dangerous. HYPERTHYROIDISM may also cause palpitations, which go away with treatment for the hyperthyroidism.

An ELECTROCARDIOGRAM (ECG) provides the necessary information to determine whether palpitations indicate an arrhythmia or other heart problem. A Holter monitor (24-hour recording of the heart's electrical activity) and an exercise STRESS TEST help identify arrhythmias and conduction disorders that are intermittent or brought on by physical exertion. Unless there is a significant underlying arrhythmia disorder, there is no need to treat palpitations. MEDITATION, relaxation techniques, and eliminating substances that can have a stimulant effect on the heart often reduce or end the palpitations.

See also PREMATURE VENTRICULAR CONTRACTION (PVC); LONG QT SYNDROME (LQTS); WOLFF-PARKINSON-WHITE SYNDROME.

paroxysmal atrial tachycardia (PAT) An ARRHYTHMIA disorder, also called paroxysmal supraventricular tachycardia (PSVT), in which the atria have episodes of rapid, regular contractions. "Paroxysmal" means the symptoms start and stop abruptly, without apparent cause. During a PAT episode, the HEART RATE may reach 140 beats per minute. The atrial contractions of PAT originate in the atrium above the ATRIOVENTRICULAR (AV) NODE rather than in the SINOATRIAL (SA) NODE that usually initiates the heart's electrical pacing impulses.

The normal path for pacing impulses is from the SA node through the atria to the AV node. Many people who have PAT have more than one conduction pathway at the AV node. Errant electrical impulses from myocardial cells in the atrium can activate the alternate pathway, called an accessory pathway, triggering atrial contractions. These are called reentrant atrial tachycardias; PAT is one variation. An episode of PAT may last a few minutes or several days. The longer the episode lasts, the more likely it is to produce symptoms.

The primary symptoms of PAT are PALPITATIONS and lightheadedness, dizziness, or SYNCOPE (fainting). Some people experience CHEST PAIN, fatigue, and shortness of breath during an episode of PAT, though feel fine otherwise. Diagnosis is by ELECTROCARDIOGRAM (ECG), which may require Holter monitor to capture episodes as they occur. Treatment may include medications that can disrupt the accessory AV pathway, such as adenosine or calcium channel blockers. RADIOFREQUENCY ABLATION, which destroys a small portion of the conductive pathway to prevent electrical impulses from traveling it, is often a viable treatment option for people with recurrent PAT and usually puts a permanent end to the episodes.

See also ATRIAL FIBRILLATION; HEART; MEDICATIONS TO TREAT CARDIOVASCULAR DISEASE.

percutaneous transluminal coronary angioplasty (PCTA) See ANGIOPLASTY.

pericarditis INFLAMMATION of the PERICARDIUM, the membranous sac that surrounds and protects the HEART. Pericarditis can be acute (comes on suddenly) or chronic (intermittent symptoms over a period of time), the result of an INFECTION or an autoimmune disorder such as RHEUMATOID ARTHRITIS. Infections are usually viral, with the coxsackie VIRUS and echovirus the most common culprits, though viral pericarditis may follow INFLUENZA or accompany AIDS. Bacterial pericarditis is less common and may occur after bacterial infection elsewhere in the body (such as STREP THROAT) or as a complication of an OPEN HEART SURGERY. Pericarditis may also develop after HEART ATTACK as an inflammatory response, typically with symptoms that begin within five days of the heart attack. Chronic pericarditis generally results from inflammatory processes not related to infection. Certain cancers, notably LEUKEMIA and KAPOSI'S SARCOMA, can involve the pericardium, causing ongoing or intermittent symptoms.

Any CHEST PAIN that persists longer than five minutes, especially pain that radiates into the arm and back, requires emergency medical evaluation to rule out HEART ATTACK.

The primary symptoms of pericarditis are PAIN from the chest, usually that radiates to the back or into the upper arm and shoulder, COUGH, and shortness of breath. Pain is usually sharp, worse with BREATHING in or lying down and relieved when sitting or standing upright. These symptoms are initially difficult to distinguish from heart attack, and typically result in emergency medical evaluation to determine whether heart attack is taking place. Many people have FEVER with acute pericarditis, and upon AUSCULTATION (listening to the chest with a STETHOSCOPE) the doctor can hear a characteristic sound called a friction rub. The pain of pericarditis comes from the pericardium, not the heart, a result of the pericardium rubbing against the heart or the LUNGS and chest cavity.

A potentially life-threatening complication of pericarditis is the rapid accumulation of fluid in the pericardial space, a filmy envelope in the pericardium's inner layer that normally contains a small amount of fluid to lubricate the beating heart. The fibrous outer pericardium does not have much ability to stretch to accommodate increased fluid, so the fluid instead pushes inward against the heart. The pressure restricts the heart's ability to contract to fill with BLOOD, resulting in a dangerous condition called cardiac tamponade. BLOOD PRESSURE and HEART RATE drop perilously in cardiac tamponade, and the compression can cause the heart to stop beating entirely. Some increase in fluid usually occurs with pericarditis, as that is part of the body's protective response to inflammation. When gradual and limited, such fluid increase does not usually affect the heart's function as the pericardium can slowly expand in response.

The diagnostic path includes ELECTROCARDIOGRAM (ECG), which reveals any arrhythmias or strain on the heart, and ECHOCARDIOGRAM to visualize the heart and its related structures. Echocardiogram usually shows the inflammation and any fluid accumulation, and helps distinguish pericarditis from other conditions such as heart attack or restrictive HEART FAILURE. Additional imaging procedures may include COMPUTED TOMOGRAPHY (CT) SCAN or MAGNETIC RESONANCE IMAGING (MRI). Treatment may include NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) to relieve inflammation and pain, or CORTICOSTEROID MEDICATIONS if the inflammation is severe. Pericardiocentesis, in which the doctor uses a long needle and syringe to withdraw fluid from the pericardium, is necessary when fluid accumulation pressures the heart. Pericardiocentesis can determine whether the pericarditis is bacterial, in which case the doctor administers ANTIBIOTIC MEDICATIONS as well.

Most people who do not have underlying CARDIOVASCULAR DISEASE (CVD) or other significant systemic conditions make full and complete recovery within two or three weeks. Pericarditis can complicate cardiovascular disease. Systemic AUTOIMMUNE DISORDERS or inflammatory conditions may result in chronic pericarditis that may require ongoing anti-inflammatory therapy, usually with NSAIDs.

See also BACTERIA; CARDIOVASCULAR DISEASE PREVENTION; CORONARY ARTERY BYPASS GRAFT (CABG);

ENDOCARDITIS; HIV/AIDS; MYOCARDITIS; TAMPONADE, CARDIAC.

pericardium A tough, two-layer membranous sac that encloses the HEART. The pericardium's fibrous outer layer, called the fibrous pericardium, protects the heart from contact with the chest wall and other structures in the chest, including the LUNGS and the sternum. The pericardium wraps completely around the heart, extending around the bases of the great vessels (AORTA, superior and inferior VENA CAVA, pulmonary ARTERY, pulmonary VEIN) as they arise from the heart. Two ligaments attach the top of the pericardium to the back of the sternum. Other ligaments loosely connect the bottom of the pericardium to the DIAPHRAGM. These structures anchor the heart in its place in the chest.

The inner layer of the pericardium is a filmy envelope. Its two surfaces are the parietal pericardium, which contacts the fibrous pericardium, and the epicardium, which covers the MYOCARDIUM somewhat like a wet tissue. Inside the envelope is a watery fluid that lubricates the heart. The inner pericardium forms a nearly frictionless containment field for the beating heart. The pericardium is vulnerable to INFLAMMATION and INFECTION (PERICARDITIS).

For further discussion of the pericardium within the context of cardiovascular structure and function, please see the overview section "The Cardiovascular System."

See also ENDOCARDIUM; LIGAMENT.

peripheral vascular disease (PVD) ATHEROSCLEROSIS that affects the peripheral arteries, notably those in the legs. ATHEROSCLEROTIC PLAQUE infiltrates the inner wall of the arteries, the intima. This causes the intima to thicken and stiffen, restricting the FLEXIBILITY of the ARTERY as well as narrowing the passage for BLOOD (arterial lumen). PVD can affect the largest to the smallest of the peripheral arteries and is the cause of INTERMITTENT CLAUDICATION as well as often an underlying factor in ERECTILE DYSFUNCTION. NEUROPATHY of DIABETES can severely exacerbate PVD, resulting in restricted circulation and limb ischemia (oxygen deprivation) that can cause tissue death (GANGRENE). PVD due to diabetes is a leading cause of limb amputation. PVD also may contribute to HYPERTENSION (high BLOOD PRESSURE).

Symptoms and Diagnostic Path

PVD often has firmly established itself by the time symptoms manifest. Intermittent claudication—PAIN with walking—is the primary symptom of PVD affecting the lower extremities. Leg or foot pain at rest, with coolness and pallor or CYANOSIS of the limb, suggests embolism (clot or atherosclerotic fragment blocking the flow of blood). Other symptoms may include lack of sensation (PARESTHESIA) or inability to move the limb (PARALYSIS), and wounds that do not heal. In severe PVD there is sometimes a mottled appearance to the SKIN. The doctor may be unable to feel a PULSE in the leg or foot, depending on the level of the occlusion or embolism. The diagnostic path often includes Doppler ULTRASOUND examination, and sometimes MAGNETIC RESONANCE IMAGING (MRI), of the legs.

Treatment Options and Outlook

The primary thrust of treatment when symptoms are present is ANTICOAGULATION THERAPY, which may include intravenous heparin when the doctor suspects an embolism. For symptoms such as intermittent claudication or rest ischemia, the treatment is typically the oral anticoagulant warfarin or antiplatelet agents such as cilostazol to reduce the risk for clot formation. A program of progressive walking improves blood flow in the legs as well as strengthens the leg muscles so they can provide additional support for the blood vessels. Weight loss reduces pressure on the arteries. The treatment regimen often includes lipid-lowering medications in conjunction with lifestyle modifications to lower blood lipid levels, which are usually elevated in PVD. Lifestyle changes include daily physical exercise such as walking, nutritious EATING HABITS, and SMOKING CESSATION. When symptoms fail to improve with these therapeutic measures, the doctor may consider ATHERECTOMY, an OPERATION to remove segments of atherosclerotic plaque from the arterial walls. Many people who have intermittent claudication benefit from wearing support stockings, which are tight against the legs to help support the blood vessels.

PVD is a progressive condition closely linked with CORONARY ARTERY DISEASE (CAD). Therapeutic

approaches, which must include lifestyle modifications to be successful, often can slow its progress.

Risk Factors and Preventive Measures

The risk factors for PVD include smoking, other atherosclerotic disease processes such as CAD, diabetes, and HYPERLIPIDEMIA. Controlling or eliminating these factors reduces the risk for PVD. Once PVD shows symptoms, then the most effective approach is aggressive management to prevent the condition from worsening.

See also ATRIAL FIBRILLATION; CARDIOVASCULAR DISEASE PREVENTION; DEEP VEIN THROMBOSIS (DVT); WALKING FOR FITNESS.

physical exercise and cardiovascular health The influence of regular physical activity on the structures and functions of the cardiovascular system. Regular AEROBIC EXERCISE has numerous effects on the cardiovascular system, improving the heart's pumping efficiency as well as the circulation's oxygen transport to the tissues of the body. It also improves the efficiency with which cells throughout the body, and notably those of skeletal MUSCLE, use oxygen. This decreases demand on the HEART, generally slowing the HEART RATE and decreasing BLOOD PRESSURE. As well, physical activity increases INSULIN sensitivity, which helps the body maintain a healthy BLOOD lipid balance to reduce the risk for HYPERLIPIDEMIA.

PHYSICAL EXERCISE RECOMMENDATIONS

- 30 to 45 minutes of moderate physical activity five to seven days a week
- 20 to 45 minutes of vigorous physical exercise three to four days a week

Health experts consider physical inactivity to be the prime lifestyle factor contributing to most acquired CARDIOVASCULAR DISEASE (CVD). Though recommendations call for 30 minutes of moderate physical exercise daily and 30 to 45 minutes of vigorous aerobic exercise three to four times a week, fewer than 20 percent of American adults are physically active at these levels and about 20 percent get no physical exercise at all. Health experts attribute at least 250,000 of deaths from cardiovascular disease to physical inactivity. Yet the level of physical activity that could prevent these deaths is minimal, only 30 minutes a day of moderately brisk walking (a pace of 3 to 4 miles per hour).

Small amounts of moderately intense physical activity that accumulate to the recommended exercise times are equally effective as contiguous blocks of exercise time, an important finding to emerge from recent research into the relationship between physical activity and cardiovascular health. Meeting the recommended minimum activity levels could prevent as much as 40 percent of cardiovascular disease. Ideal activities for cardiovascular health include walking, bicycling, running, and swimming.

See also AEROBIC FITNESS; CARDIOVASCULAR DISEASE PREVENTION; DIET AND CARDIOVASCULAR HEALTH; DIET AND HEALTH; EXERCISE AND HEALTH; LIFESTYLE AND CARDIOVASCULAR HEALTH; WALKING FOR FITNESS.

premature ventricular contraction (PVC) An early heartbeat that causes the sensation of a skipped beat. Most often PVCs are harmless. They may occur spontaneously, without apparent cause, and are most noticeable at rest or following strenuous exercise. CAFFEINE, pseudoephedrine (a vasoconstrictor and stimulant common in cold and allergy products), NICOTINE (tobacco), and anxiety (stress) may also cause PVCs. PVCs require a doctor's evaluation when they occur

- frequently
- repeatedly over a period of time rather than in isolation
- with CHEST PAIN or discomfort
- with lightheadedness, dizziness, or SYNCOPE (fainting)

A doctor also should evaluate PVCs in anyone who has diagnosed CARDIOVASCULAR DISEASE (CVD), particularly an ARRHYTHMIA disorder. Occasionally PVCs can trigger a more serious arrhythmia such as ventricular tachycardia. An ELECTROCARDIOGRAM (ECG) can identify PVCs. Because PVCs tend to be intermittent, the doctor may use a Holter monitor ECG, which records the heart's electrical activity over a period of 24 hours.

Unless PVCs indicate a serious underlying arrhythmia, cardiologists usually do not treat them. Often, eliminating potential causes such as caffeine can put an end to the PVCs. The cardiologist may

prescribe a beta blocker for persistent PVCs, after ruling out other cardiovascular conditions.

See also ECTOPIC BEAT; MEDICATIONS TO TREAT CARDIOVASCULAR DISEASE; PALPITATIONS; SMOKING AND HEALTH.

pulmonary arteries The large BLOOD vessels that carry blood from the HEART to the LUNGS. The main pulmonary ARTERY arises from the right ventricle and immediately branches into the right and left pulmonary arteries. The pulmonary arteries are the only arteries in the body that transport deoxygenated blood. Like other arteries, however, the pulmonary arteries have sturdy, muscular walls that rhythmically contract in synchronization with the heartbeat. The pulmonary valve regulates the flow of blood from the right ventricle into the pulmonary artery.

For further discussion of the pulmonary arteries within the context of cardiovascular structure and function please see the overview section "The Cardiovascular System."

See also AORTA; VALVULAR HEART DISEASE.

pulmonary hypertension Elevated BLOOD PRESSURE in the PULMONARY ARTERIES and the arteries within the LUNGS. Pulmonary HYPERTENSION develops when the arteries in the lungs become stiff and narrowed, increasing the resistance BLOOD encounters in trying to flow through them. The condition typically starts in the smallest of arteries, the arterioles, and progressively involves larger arteries until pressure within the pulmonary arteries from the HEART also rises. Elevated pressure within the pulmonary arteries increases the force the right ventricle must exert to pump blood from the heart to the lungs. Though early in the course of the condition the right ventricle can compensate by enlarging, eventually the increased workload can lead to right HEART FAILURE.

Doctors classify pulmonary hypertension, also called pulmonary arterial hypertension (PAH), as either secondary or primary. Secondary pulmonary hypertension develops as a complication of other health conditions, notably connective tissue disorders and chronic health conditions such as CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) and PULMONARY EMBOLISM. Because it follows other health conditions that become more likely with advancing age, secondary pulmonary hypertension tends to occur more frequently in people over age 60.

CONDITIONS THAT CAN CAUSE PULMONARY HYPERTENSION

AIDS	CARDIOMYOPATHY
chronic hemolytic ANEMIA	CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)
COCAINE use	HEART FAILURE
OBSTRUCTIVE SLEEP APNEA	PULMONARY EMBOLISM
PULMONARY FIBROSIS	RHEUMATIC HEART DISEASE
scleroderma	SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)
VALVULAR HEART DISEASE	

Primary pulmonary hypertension (PPH) exists independently of other health conditions and is far less common than secondary pulmonary hypertension. Most often doctors do not know what causes PPH, though they believe in many people the condition is congenital (present at birth). Though systemic hypertension—what people think of as high blood pressure—may damage blood vessels throughout the body as well as damage the heart, pulmonary hypertension and systemic hypertension are different conditions. PPH can affect people of any age though is more common among people under age 50.

Symptoms and Diagnostic Path

The earliest symptom of pulmonary hypertension is shortness of breath (DYSPNEA), typically with exertion. As the condition progresses, symptoms may include fatigue, SYNCOPE (fainting), chest pressure or PAIN, peripheral edema (swelling of the lower legs, feet, wrists, and hands), ASCITES (fluid retention in the abdominal cavity), and PULMONARY EDEMA (fluid accumulation in the alveoli, or air sacs, in the lungs). Symptoms of advanced disease often include shortness of breath at rest, CYANOSIS (bluish hue to the SKIN and lips), and ARRHYTHMIA (abnormal HEART RATE).

The diagnostic path begins with ELECTROCARDIOGRAM (ECG), which reveals right ventricular hypertrophy (enlargement), and ECHOCARDIOGRAM, which shows the heart's changed structure and function. The right ventricle typically enlarges and its walls thicken as the pulmonary hypertension begins to cause symptoms. Other diagnostic procedures may include MAGNETIC RESONANCE IMAGING (MRI) for additional visualization of the heart, PULMONARY FUNC-

TION TESTS to assess LUNG CAPACITY and the ability of the lungs to exchange oxygen and carbon dioxide, and CARDIAC CATHETERIZATION to measure the pressure within the pulmonary arteries.

Treatment Options and Outlook

Doctors may prescribe medications such as vasodilators and calcium channel blockers to help relax the arteries in the lungs and lower resistance to the flow of blood, anticoagulant medications to lower the risk for blood clots, and diuretics ("water pills") to reduce edema. Research suggests that many people who have pulmonary hypertension have elevated levels of endothelin, an amino acid compound (peptide) naturally present in the walls of the arteries that causes them to constrict. Whether this elevation is a consequence or cause of pulmonary hypertension remains unclear, though its recognition has resulted in the development of medications called endothelin receptor antagonists. These medications relieve the symptoms of pulmonary hypertension by relaxing the walls of the arteries in the lungs. Oxygen therapy can improve the amount of oxygen that enters the blood circulation.

Treatment targets the underlying cause, to the extent possible, when pulmonary hypertension is secondary, as well as aims to lower pulmonary blood pressure. However, any damage that occurs to the heart is generally irreversible. PPH is progressive and as yet there is no curative treatment. Early diagnosis and medications can slow PPH's progression and improve QUALITY OF LIFE. Lifestyle modifications, such as WEIGHT LOSS AND WEIGHT MANAGEMENT, SMOKING CESSATION, and regular physical activity within the capacity the person's cardiovascular function allows, help keep the cardiovascular system functioning as efficiently as possible. LUNG TRANSPLANTATION may be a treatment option for younger people when PPH is the only significant health condition. People who also have severe heart failure may benefit from a combined heart–lung transplantation. These are complex operations, however, and donor organs are extremely limited.

Risk Factors and Preventive Measures

The risk factors for secondary pulmonary hypertension are the conditions that may cause it. Early diagnosis and appropriate treatment for these conditions helps prevent pulmonary hypertension from developing. Because doctors do not know what causes PPH, they cannot identify clear risk factors.

See also CARDIOVASCULAR DISEASE PREVENTION; MEDICATIONS TO TREAT CARDIOVASCULAR DISEASE; ORGAN TRANSPLANTATION; OXYGEN–CARBON DIOXIDE EXCHANGE.

pulmonary veins The large blood vessels that bring blood to the left side of the HEART from the LUNGS. The main pulmonary veins arise from the lungs and branch immediately into the right pulmonary vein and the left pulmonary vein. The right pulmonary vein carries blood from the right lung and the left pulmonary vein carries blood from the left lung. The pulmonary veins are the only veins in the body that transport oxygenated blood.

For further discussion of the pulmonary veins within the context of cardiovascular structure and function, please see the overview section "The Cardiovascular System."

See also AORTA; VENA CAVA.

pulse The pattern of contractions in the arteries as BLOOD passes through them, typically synchronized with the contractions of the HEART. Where an ARTERY is close to the surface, it is possible to feel the pulse by applying pressure with two fingers (but not the thumb, which has its own perceptible pulse).

PULSE POINTS

Artery	Body Location
abdominal aorta	solar plexus area of the abdomen
brachial	inside of the upper arm
carotid	each side of the neck, below the jaw
femoral	groin
pedal	top of the foot
popliteal	behind the knee
radial	wrist, below the base of the thumb
temporal	side of the forehead
tibial	inside of the lower leg, behind the inner ankle
ulnar	wrist, at the base of the hand on the opposite side from the thumb

ARRHYTHMIAS in which the heart contracts but does not eject blood with the contraction, such as with some tachycardias, may result in a disparity between the pulse and the heart rate. The nature of the pulse aids in diagnosis:

- An ***alternating pulse*** has a regular rhythm though some beats are strong and others are weak. It may suggest left HEART FAILURE.
- A ***bigeminal pulse*** is a pattern of two beats, a strong beat then a weak beat with a long pause after. It suggests PREMATURE VENTRICULAR CONTRACTIONS (PVCS).
- A ***bounding pulse*** may be rapid and forceful. It may indicate HYPERTENSION, FEVER, ANEMIA, or RENAL FAILURE. A bounding pulse also may occur following intense physical exercise, in which case it is normal.
- A ***rapid pulse,*** also called an accelerated pulse, indicates tachycardia (heart rate of 100 beats per minute or faster). It may suggest an arrhythmia, cardiovascular SHOCK, fever, HYPERTHYROIDISM, or CORONARY ARTERY DISEASE (CAD). A rapid pulse also may occur normally following intense physical exercise.
- A ***trigeminal pulse*** is a pattern of two equally strong beats then a third weak beat with a long pause after. It may suggest CARDIOMYOPATHY.
- A ***water-hammer pulse*** is a pattern in which there is a rapid surge of blood at the pulse point followed by a complete collapse of the artery. It suggests aortic regurgitation, a condition in which the aortic valve fails to close after the left ventricle pumps blood into the aorta, allowing blood to flow back into the heart.

The characteristics of the pulse change with fitness level and age. People who exercise regularly and people who are over age 70 tend to have slower pulse rates than people who are sedentary or young. The average resting pulse for an adult is 60 to 100 beats per minute. Children typically have more rapid pulse rates. The pulse rate also temporarily increases with fever, PAIN, and anxiety.

See also BLOOD PRESSURE; HEART SOUNDS; TRADITIONAL CHINESE MEDICINE (TCM).

R

radiofrequency ablation A therapeutic procedure to treat ARRHYTHMIA disorders such as WOLFF-PARKINSON-WHITE SYNDROME or PAROXYSMAL ATRIAL TACHYCARDIA (PAT). Radiofrequency ablation uses high-frequency energy, similar to microwave energy, to destroy abnormal electrical pathways in the HEART. The cardiologist performs radiofrequency ablation via CARDIAC CATHETERIZATION, threading a catheter through a blood vessel and into the heart. Electrodes on the tip of the catheter function somewhat as an ELECTROCARDIOGRAM (ECG), sending information about the heart's electrical activity via the catheter back to a monitor. When the catheter reaches the area of dysfunctional electrical activity, the cardiologist sends a burst of high-frequency energy through the electrodes. The energy destroys the area of myocardial tissue responsible for the dysfunction, closing the abnormal electrical pathway. The heart's regular electrical pathways then become the route for the heart's electrical pacing impulses. Radiofrequency ablation permanently ends the arrhythmia about 90 percent of the time.

See also ATRIOVENTRICULAR (AV) NODE; IMPLANTABLE CARDIOVERTER DEFIBRILLATOR (ICD); PACEMAKER; SINOATRIAL (SA) NODE.

Raynaud's syndrome A condition in which the smallest arteries, the arterioles, in the hands and the feet spasm in response to cold. The spasm interrupts the flow of BLOOD to the fingers and toes, depriving them of oxygen. Raynaud's syndrome may be idiopathic (without identifiable cause) or secondary to other health conditions (notably connective tissue disorders). Raynaud's syndrome may also develop as a SIDE EFFECT of certain medications such as vasoconstrictors (drugs that cause the blood vessels to constrict). Cigarette smoking is often a precipitating factor and worsens symptoms. Some doctors use the terms *Raynaud's disease* to identify idiopathic Raynaud's and *Raynaud's phenomenon* to identify secondary Raynaud's.

POSSIBLE CAUSES OF RAYNAUD'S SYNDROME

cigarette smoking	dermatomyositis
electrical shock	ergot medications
FROSTBITE or HYPOTHERMIA	long-term exposure to vibration
PERIPHERAL VASCULAR DISEASE (PVD)	REPETITIVE MOTION INJURIES
RHEUMATOID ARTHRITIS	SCLERODERMA
SPINAL CORD INJURY	
SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)	

The doctor generally makes the diagnosis on the basis of the pattern of symptoms, which is distinctive and consistent. The pattern includes three phases most easily identified according to the color of the fingers or toes:

1. Cold causes the arterioles to spasm, depriving the fingers or toes of oxygen. The fingers or toes turn white.
2. The veins and capillaries dilate, flooding the tissues with deoxygenated blood. The fingers or toes turn blue (CYANOSIS) and typically feel numb.
3. With warmth the arterioles will relax, which restores the flow of circulation and floods the fingers or toes with oxygenated blood. The fingers or toes turn deep red, and may throb and feel hot.

The most effective treatment for Raynaud's syndrome is keeping the fingers and toes warm to prevent the arterioles from spasming. When an attack occurs, warming the fingers or toes gener-

ally restores normal circulation and ends the symptoms. Stress and anxiety may sometimes initiate the symptoms. Relaxation methods such as MEDITATION are helpful when this is the case. BIOFEEDBACK is effective for some people, and regular physical exercise helps maintain circulation. When Raynaud's syndrome fails to respond to preventive and lifestyle measures, doctors may prescribe medications such as beta blockers, calcium channel blockers, or topical nitroglycerin to relax the arterioles. Treating any underlying conditions helps mitigate the symptoms of Raynaud's syndrome.

See also MEDICATIONS TO TREAT CARDIOVASCULAR DISEASE; NEUROPATHY; PULMONARY HYPERTENSION; SMOKING AND CARDIOVASCULAR DISEASE.

risk factors for cardiovascular disease The circumstances that make a person more or less likely to develop conditions affecting the HEART and cardiovascular system. A risk factor may be fixed, or immutable, such as age, ethnicity, or gender. Other risk factors are variable, or mutable. These are the risk factors that an individual can influence, such as dietary habits and physical activity. Doctors also use the terms *alterable* and *nonalterable*, respectively. Other health conditions may also become risk factors for CARDIOVASCULAR DISEASE (CVD), notably DIABETES. Certain cardiovascular conditions, such as HYPERTENSION (high BLOOD PRESSURE) and ATHEROSCLEROSIS, are risk factors for other cardiovascular conditions such as STROKE and HEART ATTACK.

CARDIOVASCULAR DISEASE RISK FACTORS

Fixed	Variable
male	cigarette smoking
age 60 and older	OBESITY
genetic predisposition	physical inactivity
African American heritage	HYPERLIPIDEMIA (elevated blood lipid levels)
Native American heritage	HYPERTENSION (high BLOOD PRESSURE)
female postmenopause	DIABETES

More than 90 percent of cardiovascular disease among Americans develops over decades, the consequence of interactions between genetic predisposition and lifestyle. Health experts believe lifestyle choices can prevent nearly all of such acquired cardiovascular disease, even when there are genetic influences. The HUMAN GENOME PROJECT, the mapping of the human genome, has broadened scientific understanding of genes and of how they influence health and disease. Researchers are better able to assess and even manipulate the interplay between certain genetic factors and lifestyle factors. One area of ongoing genetic research is ethnicity. Though the rate of CVD is significantly higher among people of certain ethnic heritages, the reasons remain unclear.

Though individuals cannot alter genetic predisposition for health conditions, they can often mitigate, through lifestyle, the ways in which such predispositions play out in their lives. A person who has a family history of early-onset atherosclerosis, for example, may mitigate the effects of this genetic predisposition through daily moderate exercise (aerobic and STRENGTH) and dietary habits that limit fat consumption to less than 10 percent of daily calories and increased fiber consumption, as well as through maintaining healthy body weight. Other preventive measures may include frequent blood lipid level screening (every 6 to 12 months) and lipid-lowering medications for lipid levels that remain elevated despite lifestyle efforts to keep them low. These lifestyle efforts can minimize, and often prevent, cardiovascular disease.

An important dimension to risk factors for CVD is the interplay that exists among them. Physical inactivity is a key element in the development and progression of HYPERLIPIDEMIA, type 2 DIABETES, OBESITY, and hypertension. Hyperlipidemia lays the foundation for atherosclerosis, which progresses to CORONARY ARTERY DISEASE (CAD). CAD causes ISCHEMIC HEART DISEASE (IHD) and is the leading cause of heart attack. Hypertension, alone though especially in combination with atherosclerosis (CAD or PVD), is the leading cause of stroke.

Congenital heart conditions, even those repaired in early childhood, may predispose people to other forms of cardiovascular disease later in life. Adults under age 30 are the first generation for whom surgical correction of congenital heart defects was a viable treatment option. Doctors do not yet know the extent to which these anomalies may affect future cardiovascular risk.

Many health experts question whether the risk of age is more a reflection of cumulative variable risks than itself an independent risk factor. Targeting individual risk factors early in life, before substantial cardiovascular disease develops, is the most effective preventive measure. Once a cardiovascular condition begins, preventive efforts shift focus to slow the progression of disease.

See also CALORIE; CARDIOVASCULAR DISEASE PREVENTION; DIET AND CARDIOVASCULAR HEALTH; PHYSICAL EXERCISE AND CARDIOVASCULAR HEALTH; SMOKING AND CARDIOVASCULAR DISEASE.

rheumatic heart disease Damage to the valves of the HEART as a consequence of rheumatic FEVER, which develops as a complication of untreated or undertreated STREP THROAT. Streptococcal BACTERIA attack the heart valves, most commonly the mitral and aortic valves, which can leave them scarred and deformed. Rheumatic fever and rheumatic heart disease are now uncommon as ANTIBOTIC MEDICATIONS so successfully treat strep infections involving the THROAT. In the 1950s rheumatic heart disease was the leading cardiovascular cause of disability and death among American adults. Today, rheumatic heart disease is much less of a threat though still affects about 2 million Americans each year, about 3,500 of whom die as a result.

Signs of CARDIOVASCULAR DISEASE (CVD) that suggest rheumatic heart disease may include clinically significant HEART MURMUR and other indications of valvular insufficiency. Doctors may suspect rheumatic heart disease as the cause when there is a recent history of sore throat or strep throat in combination with symptoms that suggest autoimmune or inflammatory disease, such as inflamed joints, and of cardiac insufficiency, such as DYSPNEA (shortness of breath). The diagnostic path typically includes ELECTROCARDIOGRAM (ECG) to evaluate any arrhythmias, which are common in VALVULAR HEART DISEASE. ECHOCARDIOGRAM or MAGNETIC RESONANCE IMAGING (MRI) allows the cardiologist to visualize and assess the heart's valves, structure, and function.

Treatment for rheumatic heart disease may involve medications to treat secondary cardiovascular conditions such as arrhythmias and HEART FAILURE, and surgical repair or replacement of damaged valves. People who have rheumatic heart disease are vulnerable to subsequent infections and require ANTIBIOTIC PROPHYLAXIS before invasive diagnostic and therapeutic procedures, and with infections such as PHARYNGITIS, to prevent ENDOCARDITIS.

See also AUTOIMMUNE DISORDERS; MEDICATIONS TO TREAT CARDIOVASCULAR DISEASE; SCARLET FEVER.

S

sexual activity and cardiovascular disease HEART ATTACK, STROKE, major HEART surgery such as CORONARY ARTERY BYPASS GRAFT (CABG) or HEART TRANSPLANTATION, or the diagnosis of a cardiovascular condition such as HYPERTENSION (high BLOOD PRESSURE) or CORONARY ARTERY DISEASE (CAD) often causes worry and fear that sexual activity may harm the heart. Such concerns are common though generally have no medical basis. Sexual intercourse requires about the same level of cardiovascular response from the body as walking up three flights of stairs. Following a cardiovascular event, most people may resume sexual activity when they regain interest.

These preparations may make the return to sexual activity more enjoyable:

- Plan sexual activity for when both partners are well rested, relaxed, and have no time constraints.
- Plan sexual activity to take place two to three hours after eating a meal, to allow digestion to take place. Digestion diverts more of the body's blood supply to the gastrointestinal tract.
- Choose a location that is comfortable and free from distractions such as the telephone or interruptions.
- Choose less strenuous positions and have extra pillows available for added support.
- Be patient and focus on the intimacy of being together.

People who have had OPEN HEART SURGERY or who have residual complications resulting from stroke may feel unsure of their physical attractiveness. Open, honest communication between partners can help put these concerns in perspective and allow each partner to express his or her feelings.

See also LIVING WITH CARDIOVASCULAR DISEASE; QUALITY OF LIFE.

sick sinus syndrome A collective term for ARRHYTHMIA disorders that arise from dysfunction of the SINOATRIAL (SA) NODE and the electrical conduction network within the HEART. The SA node may stop functioning, or there may be a disruption in the pathway for the electrical impulses the SA node generates. Generally sick sinus syndrome results in bradycardia (slow HEART RATE). Key symptoms include fatigue and SYNCOPE (fainting). Sick sinus syndrome may also be present without symptoms, in which case it does not usually require treatment. ELECTROCARDIOGRAM (ECG) reveals the abnormal electrical pacing impulses and provides the diagnosis. Treatment is nearly always an implantable PACEMAKER to maintain an adequate heart rate.

See also ATRIOVENTRICULAR (AV) NODE; BUNDLE BRANCH; BUNDLE BRANCH BLOCK; LONG QT SYNDROME (LQTS); WOLFF-PARKINSON-WHITE SYNDROME.

sinoatrial (SA) node A small cluster of specialized NERVE and MUSCLE fibers located in the upper wall of the heart's right atrium. The SA node initiates the electrical pacing impulse that causes the HEART to contract. In the healthy heart the electrical impulse spreads in an orderly and synchronized pattern through the two atria, causing them to contract. The ATRIOVENTRICULAR (AV) NODE, a second small cluster of specialized nerve and muscle fibers located in the wall of the heart between the atria and the ventricles, picks up the impulse, amplifies it, and sends it through the ventricles to cause them to contract.

For further discussion of the SA node within the context of cardiovascular structure and function please see the overview section "The Cardiovascular System."

See also BUNDLE BRANCH; BUNDLE BRANCH BLOCK; CARDIAC CYCLE; SICK SINUS SYNDROME.

smoking and cardiovascular disease CARDIOVASCULAR DISEASE (CVD) is the most frequent and significant consequence of cigarette smoking, with smoking accounting for one in six deaths due to CVD. Smoking significantly increases the risk for HYPERTENSION (high BLOOD PRESSURE), ATHEROSCLEROSIS, and CORONARY ARTERY DISEASE (CAD). The combination of cigarette smoking and using oral contraceptives (birth control pills) presents a particular risk of BLOOD clot formation in women, especially women over age 35. This raises the risk for STROKE and HEART ATTACK such that many doctors will not prescribe oral contraceptives for women who smoke. Smoking is also a key factor in numerous pulmonary diseases, affecting the cardiovascular system's ability to circulate oxygen-rich blood.

The US Surgeon General offered the first conclusive evidence of the correlations between smoking and cardiovascular disease in the landmark 1964 report, *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service*. Researchers have since continued to accumulate knowledge and understanding of the mechanisms through which smoking affects cardiovascular health. Cigarette smoke contains more than 2,000 identifiable chemicals, dozens of which are carcinogenic (CANCER-causing) or have other deleterious actions on health. Two in particular, NICOTINE and carbon monoxide, are highly toxic to the cardiovascular system.

Nicotine and Cardiovascular Function

NICOTINE is a CENTRAL NERVOUS SYSTEM stimulant that acts on nerves throughout the body. In the cardiovascular system, nicotine stimulates the nerves that regulate smooth MUSCLE tissue, causing smooth muscle cells to contract. This constricts blood vessels, notably arteries, reducing the channel for blood flow. Nicotine further stimulates the baroreflex sensors (clusters of NERVE cells in the major arteries and the heart that sense the flow and pressure of blood). These actions result in increased blood pressure, HEART RATE, and cardiac workload. Nicotine further acts as an irritant within the arteries, causing INFLAMMATION of the inner layer of the arterial wall. Researchers believe such inflammation may be the foundation for atherosclerosis.

Carbon Monoxide and Cardiovascular Function

Carbon monoxide is a poison. It has a greater affinity than oxygen for HEMOGLOBIN and binds with hemoglobin, blocking hemoglobin from carrying oxygen. This reduces the amount of oxygen that enters the bloodstream from the LUNGS. By the end of a cigarette, a smoker can have concentrations of carbon monoxide as high as 7 percent; 10 percent is the level at which symptoms of carbon monoxide poisoning begin to become apparent. Carbon monoxide in the bloodstream deprives cells in the BRAIN and heart, which rely on oxygen for fuel.

Environmental Smoke Exposure

Cigarette smoke also raises the risk for health problems, including cardiovascular disease, among people who are themselves nonsmokers though live or work in a smoking environment. Children are at particular risk. Numerous studies show the children of smokers have more EAR infections, sinus infections, and upper respiratory infections than children who live in smoke-free environments. Long-term exposure to ENVIRONMENTAL CIGARETTE SMOKE, called passive smoking, has the same health consequences as active smoking.

Smoking Cessation

The health risks of cigarette smoking diminish within 30 to 40 minutes of the last puff. With sustained SMOKING CESSATION, the risk for cardiovascular disease gradually diminishes over 5 to 10 years, finally reaching a level consistent with the risks for a nonsmoker. Any damage that has already occurred to the cardiovascular system is permanent, however.

See also ANTISMOKING EFFORTS; CARDIOVASCULAR DISEASE PREVENTION; CONTRACEPTION; HEALTH RISK FACTORS; INHALED TOXINS; LIFESTYLE AND CARDIOVASCULAR HEALTH; SMOKING AND CANCER; SMOKING AND HEALTH.

soy and cardiovascular health Soy protein appears to help lower cholesterol blood levels, particularly low-density lipoprotein cholesterol (LDL-C). The American Health Association recommends replacing animal protein with soy protein as part of a balanced, low-fat diet. People who consume 25 to 50 grams of soy protein daily can lower their LDL-C levels by as much as 8 percent. In combination with other cholesterol-lowering approaches such as increased daily exercise, soy in the diet contributes to a heart-healthy lifestyle. Soy protein contains isoflavones—notably genistein, daidzein, and glycetein—that help to reduce the formation of ATHEROSCLEROTIC PLAQUE, thus lowering the risk for ATHEROSCLEROSIS and related conditions such as CORONARY ARTERY DISEASE (CAD). Soy protein is also high in fiber, helping absorb dietary cholesterol and fats in the intestinal tract to reduce the amount that enters the blood circulation.

DIETARY SOURCES OF SOY PROTEIN

soy cheese	soy flour
soybeans (boiled or roasted)	soy milk
textured vegetable protein (TVP) products	tofu

See also CARDIOVASCULAR DISEASE PREVENTION; DIET AND CARDIOVASCULAR HEALTH; HORMONE-DRIVEN CANCERS; LIFESTYLE AND CARDIOVASCULAR HEALTH.

stent A tiny, springlike device inserted into an ARTERY to help maintain the artery's patency after ANGIOPLASTY (a CARDIAC CATHETERIZATION procedure to clear or compress ATHEROSCLEROTIC PLAQUE from the inner walls of an artery). The stent holds pressure against the artery's inner wall, maintaining compression of the plaque as well as making it difficult for the artery to constrict. Cardiologists use stents primarily in the CORONARY ARTERIES though may also use them in carotid ENDARTERECTOMY and peripheral artery angioplasty. An anticoagulant medication coats some stents, called DRUG-emitting, to discourage clot formation. Stents can extend the effectiveness of angioplasty by months to a year or more. Angioplasty with stent placement can delay the need for CORONARY ARTERY BYPASS GRAFT (CABG) or provide an acceptable alternative for people with less severe occlusions. Most stents require replacement every three to five years.

See also ANTICOAGULATION THERAPY; BLOOD; MEDICATIONS TO TREAT CARDIOVASCULAR DISEASE.

stethoscope An instrument the doctor uses to listen to sounds within the body. The cardiologist uses a stethoscope to listen to the function of the valves in the HEART, to the HEART RATE, to the flow of BLOOD through the chambers of the heart, and for abnormal sounds, such as a pericardial rub or a HEART MURMUR, that can indicate cardiovascular disorders. The French physician René Laënnec (1781–1821) invented the stethoscope and introduced the first practical model, a simple tube with a flare at one end and a small opening that served as an earpiece at the other end, in 1816. The instrument evolved over the next 100 years into the familiar style in use today, a flexible "Y" of tubing with dual earpieces and a combination bell and diaphragm with a lever to switch between them. The bell picks up low-pitched tones and the diaphragm picks up high-pitched tones.

See also AUSCULTATION.

stress test A diagnostic procedure to evaluate the cardiovascular system's ability to meet the body's increased oxygen needs during physical exercise. The most common procedure is the exercise stress test, in which the person walks on a treadmill or rides a stationary bicycle at an escalating pace. A continuous ELECTROCARDIOGRAM (ECG) monitors the heart's response. Variations of the stress test include the ECHOCARDIOGRAM stress test, in which the cardiologist uses ULTRASOUND to visualize the heart's functions during exercise, and the pharmacological stress test, in which the cardiologist administers a DRUG such as dipyridamole that causes a cardiovascular response that simulates the effects of exercise. A stress test helps determine the extent of cardiovascular impairment present as a result of conditions such as CORONARY ARTERY DISEASE (CAD) and HEART FAILURE. A stress test does not require preparation or recovery, and takes 20 to 40 minutes to complete. There is a very slight risk that a stress test may trigger a HEART ATTACK, to which the facility and its staff are prepared to respond if necessary.

See also HEART; MYOCARDIAL PERFUSION IMAGING; OXYGEN–CARBON DIOXIDE EXCHANGE.

stroke An interruption of BLOOD flow and oxygen supply to the BRAIN, sometimes called a brain attack. Stroke strikes about 700,000 Americans each year. For two thirds of them the stroke is a second or subsequent stroke. About 85 percent of strokes are ischemic; they result from blockage of an arterial pathway in the brain. The remaining 15 percent are hemorrhagic; they result from bleeding into the brain, typically from a blood vessel that ruptures. About 90 percent of people survive a first ischemic stroke, though a third of them experience permanent disability of varying severity as a consequence of the damage to the brain. The risk for death rises with each subsequent stroke. Hemorrhagic strokes are more likely to be fatal, claiming the lives of nearly half of those who have them. In 2000, about 2.4 million Americans were stroke survivors.

HYPERTENSION (high BLOOD PRESSURE) is the leading cause of stroke. Unfortunately, hypertension has no symptoms and many people do not know they have it until they suffer stroke or HEART ATTACK. Chronically elevated blood pressure stresses blood vessels, causing them to stiffen and thicken to help protect against the constant pounding of blood. This response (ARTERIOSCLEROSIS) makes the arteries vulnerable to INFLAMMATION and accumulations of debris (ATHEROSCLEROTIC PLAQUE), resulting in ATHEROSCLEROSIS. The high pressure of blood rushing through the arteries causes tiny fragments of the plaque to break free. The fragments float through the blood circulation until they lodge in a blood vessel, blocking the further flow of blood. When this occlusion happens in the heart, it causes a MYOCARDIAL INFARCTION or heart attack. In the brain, the occlusion causes stroke.

Health experts recommend annual BLOOD PRESSURE checks for all people age 50 and older, and for younger people who have risk factors for CARDIOVASCULAR DISEASE (CVD).

Brain cells require a constant supply of oxygen to meet their energy needs. Deprivation of oxygen for as little as 30 seconds causes them to begin shutting down. Lack of oxygen for two to three minutes causes brain cells to begin dying. After five minutes, enough brain cells can die to cause permanent loss of function in the affected area. This loss may involve cognitive function, memory, speech and language processing, and physical movement. The brain's correlation to the body is ipsilateral. Damage to the right brain may result in weakness or paralysis on the left side of the body; damage to the left brain may affect the right side of the body.

Time is crucial. Treatment for ischemic stroke that begins within four hours can incorporate drugs to dissolve the blocking blood clot, minimizing or preventing damage to the brain.

Symptoms and Diagnostic Path

Symptoms of stroke may be subtle or pronounced. The main symptoms of stroke include

- numbness or tingling on one side of the face or body
- difficulty speaking (including slurred speech) or swallowing
- drooping of facial features on one side
- weakness or PARALYSIS on one side of the body
- loss of vision or change in vision, particularly in only one EYE

It is important to seek medical attention without delay at the first indication that a stroke may be occurring. Early treatment with THROMBOLYTIC THERAPY can dissolve developing blood clots, mitigating or preventing the stroke. The diagnostic path typically includes COMPUTED TOMOGRAPHY (CT) SCAN or MAGNETIC RESONANCE IMAGING (MRI) to visualize the location and extent of the stroke, and to determine whether the stroke is ischemic or hemorrhagic. ELECTROENCEPHALOGRAM (EEG), which measures the brain's electrical activity, and a comprehensive NEUROLOGIC EXAMINATION can help assess the extent of damage the stroke has caused.

Treatment Options and Outlook

Immediate treatment focuses on minimizing damage to the brain. Optimally, early intervention permits thrombolytic therapy, which must begin within four hours of the stroke's onset. Treatment

beyond this window of opportunity typically includes ANTICOAGULATION THERAPY for ischemic stroke to prevent further clots from forming and supportive measures to maintain cardiovascular stability. Most people who experience strokes have hypertension, so subsequent treatment includes measures to bring blood pressure under control through medications and lifestyle changes.

People who receive thrombolytic therapy often have no residual effects from their strokes and can return to their regular activities within a few weeks. People who experience permanent disability as a result of stroke may require inpatient or outpatient rehabilitation. The level of recovery depends on the extent of damage. Many people with serious disabilities are able to learn methods for adapting to their limitations, allowing them to return to some activities and perhaps independent living. About 70 percent of people who experience strokes are able to return to functional independence and often many of their regular activities, within three to six months.

Risk Factors and Preventive Measures

The key risk factors for stroke are hypertension and atherosclerosis. Cardiovascular conditions involving clot formation present a high risk for stroke. These include DEEP VEIN THROMBOSIS (DVT), ATRIAL FIBRILLATION, CAROTID STENOSIS, and VALVULAR HEART DISEASE. DIABETES also raises the risk for stroke. Other risk factors are those for all forms of CARDIOVASCULAR DISEASE (CVD): smoking, physical inactivity, and diet high in saturated fats and excessive calories. Stroke also becomes more likely with advancing age.

The most effective preventive measure is maintaining a healthy blood pressure. All adults over age 50 should have annual blood pressure checks, with more frequent checks when blood pressure is elevated or risk factors for hypertension are present. Efforts to maintain good cardiovascular health, such as daily physical exercise and WEIGHT LOSS AND WEIGHT MANAGEMENT, help lower the risk for subsequent stroke as well as for other forms of cardiovascular disease.

See also CALORIE; CARDIOVASCULAR DISEASE PREVENTION; COGNITIVE FUNCTION AND DYSFUNCTION; ENDARTERECTOMY; HEALTH RISK FACTORS; RISK FACTORS FOR CARDIOVASCULAR DISEASE; SPEECH DISORDERS; SWALLOWING DISORDERS; TRANSIENT ISCHEMIC ATTACK (TIA).

sudden cardiac death Unexpected, fatal CARDIAC ARREST (cessation of cardiac activity). Typically there are no warning signs of impending cardiovascular crisis. Electrical dysfunction is the most frequent cause of sudden cardiac death. In young people, ARRHYTHMIA disorders such as LONG QT SYNDROME (LQTS) or WOLFF-PARKINSON-WHITE SYNDROME, or hereditary HEART conditions such as hypertrophic CARDIOMYOPATHY, are often to blame. Some health experts believe ELECTROCARDIOGRAM (ECG) should be a part of the athletic physical examination, as intense physical exertion can trigger electrical dysfunctions that result in death.

In people age 50 and older sudden cardiac death typically results from arrhythmia disorders, MYOCARDIAL INFARCTION, ISCHEMIC HEART DISEASE (IHD) that is a consequence of CORONARY ARTERY DISEASE (CAD), and HEART FAILURE. Most people who experience sudden cardiac death were unaware they had CARDIOVASCULAR DISEASE (CVD) or had been undergoing successful treatment to manage a particular cardiovascular condition such as HYPERTENSION. Because the event that causes cardiovascular collapse is generally catastrophic, resuscitative efforts tend to be unsuccessful.

See also CARDIOPULMONARY RESUSCITATION (CPR); CARDIOVASCULAR DISEASE PREVENTION; HEALTH RISK FACTORS; MARFAN SYNDROME; TORSADE DE POINTES.

syncope The temporary loss of CONSCIOUSNESS and posture, commonly called fainting. Syncope is common and can arise from numerous causes ranging from standing too long, which allows BLOOD to pool in the legs, to ARRHYTHMIA and TRANSIENT ISCHEMIC ATTACK (TIA), which interrupt the flow of blood to the BRAIN. About 10 percent of syncope episodes are the result of cardiovascular events such as arrhythmias, MYOCARDIAL INFARCTION, MICROINFARCTION, HYPOTENSION, and TIA.

Any episode of syncope in a person who has a history of HEART ATTACK, STROKE, ARRHYTHMIA, or other known CARDIOVASCULAR DISEASE (CVD) requires immediate medical evaluation.

Other causes of syncope include neurologic events (such as vasovagal response), medication side effects, heat, DEHYDRATION, fear, FEVER, and PREGNANCY. Most people regain consciousness within a few seconds to three minutes. Syncope may be an isolated event or a symptom of underlying health concerns. A doctor should evaluate recurrent episodes of syncope. Such an evaluation typically includes a NEUROLOGIC EXAMINATION and an ELECTROCARDIOGRAM (ECG).

See also ADVERSE REACTION; CRANIAL NERVES; GASTROPARESIS; SEIZURE DISORDERS; UNCONSCIOUSNESS.

T

tachycardia See ARRHYTHMIA.

tamponade, cardiac A life-threatening compression of the HEART that prevents it from expanding to fill with BLOOD. Cardiac tamponade is most often a complication of PERICARDITIS and develops when fluid rapidly accumulates within the layers of the PERCARDIUM. The pericardium's fibrous outer layer does not readily expand, which forces the fluid to press inward against the heart. Without immediate action to drain the fluid, the heart will stop beating. ELECTROCARDIOGRAM (ECG) demonstrates the characteristic patterns of electrical changes in the heart's rhythm that strongly indicate cardiac tamponade. COMPUTED TOMOGRAPHY (CT) SCAN or MAGNETIC RESONANCE IMAGING (MRI) can confirm the diagnosis. Generally the doctor can aspirate (withdraw) the fluid using a needle and syringe (pericardiocentesis), which relieves the pressure and allows the heart to resume normal function. Surgery to create an opening in the pericardium may be necessary to manage cardiac tamponade that occurs with chronic pericarditis. Penetrating trauma that causes bleeding into the pericardium may also cause cardiac tamponade.

See also MYOCARDIAL INFARCTION.

thrombolytic therapy Emergency treatment with medications to dissolve BLOOD clots that are in the process of forming. When initiated promptly, thrombolytic therapy can avert MYOCARDIAL INFARCTION or ischemic (nonhemorrhagic) STROKE, mitigating damage to the HEART or BRAIN respectively. Doctors also may use thrombolytic therapy to treat blood clots that form elsewhere in the body, such as in the leg (DEEP VEIN THROMBOSIS [DVT]) or the LUNGS (PULMONARY EMBOLISM).

Thrombolytic agents act by converting plasminogen, an inactive protein in the blood circulation, to plasmin, an active protein that breaks down the key proteins that form blood clots (fibrinogen and fibrin). These agents can only act before the clot fully forms and hardens, which establishes a therapeutic window of about four hours from the onset of clot formation. Early diagnosis is therefore essential.

COMMON THROMBOLYTIC AGENTS

alteplase (aPA)	anisoylated purified streptokinase activator complex (APSAC)
anistreplase	streptokinase
tissue plasminogen activator (tPA)	urokinase

The oldest of the thrombolytic agents is streptokinase, which doctors began using in the 1940s. Streptokinase and anistreplase derive from streptococcal BACTERIA. When administered, these agents initiate ANTIBODY production. The antibodies become active after five days and remain active for about six months. During that timeframe, doctors cannot re-administer streptokinase or anistreplase. Some people also have adverse responses to these agents, especially streptokinase. Laboratories manufacture most of the newer thrombolytic agents using recombinant technology, which nearly eliminates these immune responses.

The most significant risk of thrombolytic therapy is uncontrolled bleeding (HEMORRHAGE). For this reason, it is crucial for doctors to determine whether a stroke is ischemic (caused by a clot) or hemorrhagic (caused by bleeding) before administering a thrombolytic agent. For venous clots, such as with deep vein thrombosis, the doctor may directly inject the agent into the clot. For arterial

clots, such as with myocardial infarction or stroke, the doctor injects the agent into a vein for distribution throughout the circulation. Thrombolytic agents remain active in the bloodstream for 15 to 90 minutes, depending on the agent. With prompt initiation of thrombolytic therapy, the agent dissolves the clot and the person experiences little or no adverse effects as a consequence of the thrombolytic event.

See also ANTICOAGULANT THERAPY; IMMUNE RESPONSE.

torsade de pointes A life-threatening ventricular tachycardia (rapid contractions of the ventricles) that is the most serious complication of the ARRHYTHMIA disorder LONG QT SYNDROME (LQTS). Torsade de pointes is a distinctive pattern of QRS complex electrical activity, QRS being the points on the ELECTROCARDIOGRAM (ECG) that identify ventricular contraction.

The term "torsade de pointes" means "twisting around the points." In ballet, the term's origination, the term identifies a movement in which multiple steps rotate the dancer around an imaginary axis. On the ECG, the QRS complex appears to twist around the electrical baseline with a continuously changing point of origin, reminiscent of the ballet movement. The pattern represents a progressive change in myocardial cell polarity (abnormal shifts in the cell's electrical charge), a marked dysfunction of the heart's electrical pacing and conduction mechanisms. Unless interrupted, torsades de pointes results in SUDDEN CARDIAC DEATH.

The ECG provides definitive diagnosis. Torsade de pointes may stop spontaneously or may require emergency medical intervention such as DEFIBRILLATION (electrical shock to restore normal rhythm) or a temporary PACEMAKER. Numerous medications can cause acquired LQTS and consequently torsade de pointes, including the commonly prescribed antibiotic erythromycin, ANTIPSYCHOTIC MEDICATIONS such as the phenothiazines, and most drugs that affect the heart's function such as those to treat arrhythmias, HEART FAILURE, and HYPERTENSION (high BLOOD PRESSURE). COCAINE also can cause torsade de pointes. Stopping the causative DRUG typically ends the torsade de pointes.

See also HEART; HYPOCALCEMIA; HYPOKALEMIA; MEDICATIONS TO TREAT CARDIOVASCULAR DISEASE.

transient ischemic attack (TIA) A brief, episodic interruption of the flow of BLOOD to the BRAIN, often called a mini-STROKE. The most common cause of a TIA is a fragment of ATHEROSCLEROTIC PLAQUE or a BLOOD clot that breaks free and travels through the blood circulation until it lodges in an ARTERY or arteriole. TIAs also can be hemorrhagic, the result of small ruptures in the tiny arteries in the brain, often a consequence of untreated HYPERTENSION (high BLOOD PRESSURE) and CAROTID STENOSIS (narrowing and occlusion of the carotid artery in the neck). ATRIAL FIBRILLATION and VALVULAR HEART DISEASE are other common sources of clots.

Symptoms of TIA are brief and temporary and may include

- episodes of SYNCOPE (loss of CONSCIOUSNESS) or "freezing," in which the person appears conscious and alert but does not respond
- episodes of tingling or numbness affecting the face or parts of the body such as the fingers or hand, typically only on one side of the body
- temporary inability to use the arm or leg, or both, on one side of the body
- lapses in cognitive function or memory

TIAs are more common in people over age 70. Doctors generally consider them to be warning signs of impending stroke. Early diagnosis and therapeutic intervention can help avert full-fledged stroke. The diagnostic path typically includes imaging procedures such as COMPUTED TOMOGRAPHY (CT) SCAN or MAGNETIC RESONANCE IMAGING (MRI). Treatment may include ANTICOAGULATION THERAPY to reduce the blood's tendency to clot as well as medications to treat arrhythmias (notably atrial fibrillation), hypertension, and HYPERLIPIDEMIA (elevated blood lipid levels), if these conditions are present. The cardiologist may recommend carotid ENDARTERECTOMY when carotid stenosis is a causative factor.

See also ARRHYTHMIA; CARDIOVASCULAR DISEASE PREVENTION; COGNITIVE FUNCTION AND DYSFUNCTION; MICROINFARCTION.

transmyocardial laser revascularization (TMLR) A treatment for ANGINA PECTORIS and ISCHEMIC HEART DISEASE (IHD) in which the cardiovascular surgeon

uses a laser to create several dozen tiny channels through the wall of the heart's left ventricle to improve the flow of BLOOD and oxygen to the MYOCARDIUM (heart MUSCLE). The surgeon makes a small "window" incision through the ribs to gain access to the myocardium, and the HEART continues to beat during the surgery. The channels allow blood to flow directly from the ventricle's chamber to the muscle tissue. Researchers do not know why TMLR relieves angina pectoris, though believe it allows oxygen to directly enter myocardial cells and also encourages new blood vessels to grow (collateral circulation). Cardiologists generally use TMLR only when other treatments for angina have failed or are not feasible. Most people stay in the hospital for three to seven days following surgery and are able to return to their regular activities, including work, in four to eight weeks.

See also CORONARY ARTERY BYPASS GRAFT (CABG); SURGERY BENEFIT AND RISK ASSESSMENT.

triglycerides blood level The amount of the fatty acid group, triglycerides, that is present in the BLOOD circulation. Most of the body's fats are in the chemical form of triglycerides, which provide the body with energy. The cells draw triglycerides from the blood to meet their immediate energy needs. The body acquires triglycerides from dietary sources as well as manufactures them. During digestion the gastrointestinal tract extracts triglycerides from dietary saturated fats such as are abundant in meats. When the level of triglycerides in the blood meets or exceeds the body's needs, the LIVER converts excess CALORIES that derive from any dietary source into triglycerides. The body stores excess triglycerides in fat cells, drawing from these stored energy supplies when demand, such as increased physical activity, exceeds the triglycerides available in the blood circulation.

In general, blood triglyceride levels rise when CHOLESTEROL BLOOD LEVELS, and particularly low-density lipoprotein cholesterol (LDL-C), are elevated. Blood triglyceride levels also tend to be elevated in OBESITY and DIABETES. The role elevated blood triglyceride levels play in CARDIOVASCULAR DISEASE (CVD) remains unclear. The National Cholesterol Education Program (NCEP), a consensus group of health experts, has established healthy and unhealthy levels of triglycerides in the blood based on correlations between elevated levels and cardiovascular conditions such as ATHEROSCLEROSIS, CORONARY ARTERY DISEASE, (CAD), and PERIPHERAL VASCULAR DISEASE (PVD), as people who have these conditions typically have elevated blood triglycerides as well.

Doctors recommend lifestyle modifications such as reducing dietary saturated fat and ALCOHOL consumption, increased daily exercise, and WEIGHT LOSS AND WEIGHT MANAGEMENT when triglyceride levels are slightly elevated (marginal) and often prescribe lipid-lowering medications when triglyceride levels are high or very high. Some people have elevated triglyceride blood levels and healthy cholesterol blood levels. For them, doctors recommend vigilance to maintain healthy cholesterol blood levels and annual monitoring, along with lifestyle habits that support overall cardiovascular health.

TRIGLYCERIDE BLOOD LEVELS (MILLIGRAMS PER DECILITER)

less than 150 mg/dL	healthy
150 to 199 mg/dL	marginal
200 to 499 mg/dL	high
500 mg/dL or higher	very high

See also CALORIE; DIET AND CARDIOVASCULAR HEALTH; DIET AND HEALTH; HYPERLIPIDEMIA; MEDICATIONS TO TREAT CARDIOVASCULAR DISEASE; NUTRIENTS.

V–W

valvular heart disease The collective term for the malformations and disorders that can affect the valves of the HEART. Valvular heart disease may affect any of the heart's four valves: mitral, pulmonary, aortic, and tricuspid. The most common forms of valvular heart disease are

- stenosis, in which the valve does not open completely
- regurgitation, also called incompetence or insufficiency, in which the valve does not close completely
- prolapse, affecting primarily the mitral valve, in which the valve leaflets are irregularly shaped such that they bulge when they close

POSSIBLE CAUSES OF VALVULAR HEART DISEASE

ANKYLOSING SPONDYLITIS	atrial septal defect (ASD)
bicuspid aortic valve	calcification
CONGENITAL ANOMALY	CORONARY ARTERY DISEASE (CAD)
ENDOCARDITIS	GRAVES'S DISEASE
HEART ATTACK	hypertrophic CARDIOMYOPATHY
MARFAN SYNDROME	MUSCULAR DYSTROPHY
PULMONARY HYPERTENSION	RHEUMATIC HEART DISEASE
RHEUMATOID ARTHRITIS	SICKLE CELL DISEASE
SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)	ventricular septal defect (VSD)

Until the 1950s, valvular heart disease was the leading cardiovascular cause of death, and RHEUMATIC HEART DISEASE, a complication of streptococcal INFECTION such as STREP THROAT, was the most frequent cause of valvular heart disease. As ANTIBIOTIC MEDICATIONS became the standard of treatment for strep throat and other infections, rheumatic heart disease and correspondingly valvular heart disease declined dramatically. Though rheumatic heart disease still accounts for about half of valvular heart disease, other causes include congenital malformations and degenerative effects that accompany aging.

Symptoms and Diagnostic Path

Many people who have valvular heart disease do not have symptoms until damage to the heart becomes significant, progressing to HEART FAILURE, CARDIOMYOPATHY, and ARRHYTHMIA. When symptoms are present, they may include

- tiredness or fatigue
- shortness of breath, especially with exertion
- periods of lightheadedness
- chest tightness or discomfort
- PALPITATIONS

Often, the underlying valve malformation (congenital or acquired) exists for years to decades before affecting the valve's function to the extent of causing symptoms. Sometimes the doctor detects valvular heart disease before symptoms are present, commonly by hearing a HEART MURMUR during a ROUTINE MEDICAL EXAMINATION. Though many heart murmurs are occasional and innocent (not indicating any disease), certain valve disorders produce distinctive murmurs. Other procedures likely along the diagnostic path include ELECTROCARDIOGRAM (ECG), ECHOCARDIOGRAM, and COMPUTED TOMOGRAPHY (CT) SCAN or MAGNETIC RESONANCE IMAGING (MRI). Depending on the person's general cardiovascular status, the cardiologist may also recommend CARDIAC CATHETERIZATION.

Treatment Options and Outlook

Medications can control much valvular heart disease. Those commonly prescribed include antico-

agulants to reduce the risk for blood clots and beta blockers or calcium channel blockers to lower BLOOD PRESSURE and slow the HEART RATE. When heart failure or cardiomyopathy is also present, the cardiologist may prescribe digoxin to strengthen the heart's contractions and diuretic medications to reduce or prevent excessive fluid accumulation in the body tissues. Lifestyle efforts, such as nutritious EATING HABITS and daily physical exercise, are important to improve overall cardiovascular status. SMOKING CESSATION and weight loss, if appropriate, are essential to reduce the risk for further CARDIOVASCULAR DISEASE (CVD).

Surgery becomes a treatment option when medical efforts are unsuccessful or valve damage is significant. Surgical options include repair (valvuloplasty) or replacement (prosthetic valve).

Valvuloplasty Balloon valvuloplasty is a procedure to treat stenosis in which the cardiologist uses cardiac catheterization to thread a catheter with a tiny balloon on the tip through a blood vessel and into the heart. When the catheter tip is in position in the valve's opening, the cardiologist inflates the balloon to gently expand the opening. Operative valvuloplasty involves OPEN HEART SURGERY to gain access to the diseased valve. The surgeon may use various methods to repair the valve, depending on the valve and the nature of the damage.

Valve replacement The surgeon may replace a damaged valve that is beyond repair. Prosthetic heart valves fall into two general categories, tissue and mechanical. Tissue valves come from human cadaver donors or animal tissues. Animal valves are typically porcine (pig) or bovine (cow) and are sterilized and processed before use. The advantage to tissue valves is that they function in the same manner as the native valve. The disadvantage is that they wear out. Mechanical valves are made of materials such as stainless steel and high-tech plastics. Their main advantage is that they are completely inert and last a very long time. After receiving a prosthetic heart valve the person must take ANTICOAGULATION THERAPY for life and take prophylactic antibiotics before invasive dental, surgical, or diagnostic procedures. Prosthetic valves, whether tissue or mechanical, are prone to collecting blood clots. A valve replacement OPERATION is also open heart surgery.

Risk Factors and Preventive Measures

Adults who are over the age of 40 may have had rheumatic FEVER or rheumatic heart disease as children and may be vulnerable to valvular heart disease as a result. Most people under the age of 40 receive antibiotic medications as the standard course of treatment for strep throat, which has greatly reduced the spread of the infection to the heart. Despite these advances, however, nearly 20,000 Americans a year die from valvular heart disease. It remains essential to receive prompt and appropriate treatment for strep infections as well as for early indications of valvular heart disease. People who know or believe they had rheumatic fever in childhood should make sure their doctors are aware of this when having routine medical examinations or receiving treatment for other cardiovascular conditions.

See also CARDIOPULMONARY BYPASS; CARDIOVASCULAR DISEASE PREVENTION; CONGENITAL HEART DISEASE; LIVING WITH CARDIOVASCULAR DISEASE; OBESITY AND CARDIOVASCULAR DISEASE; WEIGHT LOSS AND WEIGHT MANAGEMENT.

varicose veins Distended and distorted veins, typically occurring in the legs. Varicose veins indicate dysfunctional venous valves, which allow BLOOD to backflow or to pool in the VEIN when standing or sitting (VENOUS INSUFFICIENCY). There appears to be a GENETIC PREDISPOSITION for varicose veins, in that they seem to run in families. Varicose veins become more common with increasing age, as the blood vessels lose elasticity and other health conditions become contributing factors. Women are more likely than men to develop varicose veins, though men and women who spend a lot of time standing are at increased risk for varicose veins.

Varicose veins appear enlarged and twisted beneath the skin's surface, most noticeably on the lower legs. For many people, varicose veins are more of a cosmetic than a health concern. Some people experience leg cramps, soreness, and itching. Severe varicose veins result in extensive blood pooling that can cause changes in SKIN color or skin ulcers (venous stasis ulcers) to develop. Most varicose veins respond to conservative treatment such as frequent elevation to relieve the pressure gravity exerts on blood flow. Regular walking

tones and strengthens the muscles of the legs, which then can help to support the veins. The rhythmic movement of the leg muscles during walking also helps push blood through the veins.

Treatment for severe varicose veins may include sclerotherapy, in which the doctor injects a chemical into the varicose vein that causes the vein to SCAR and close. Blood reroutes to other veins, and the varicose vein gradually shrinks and fades to become barely noticeable. LASER SURGERY is effective on smaller varicose veins. For large varicose veins that generate significant PAIN or are causing skin ulcers, the doctor may surgically remove the affected veins in a procedure commonly called vein stripping.

The main complication of varicose veins is DEEP VEIN THROMBOSIS (DVT), in which blood clots form in the pooled or slow-moving blood. The clots cause localized pain and swelling, and if they break free can lodge in the LUNGS, causing PULMONARY EMBOLISM, or in the BRAIN, causing STROKE. Preventive measures include frequent walking, wearing low-heeled shoes (which exercise the muscles in the lower leg), shifting the weight from leg to leg and rocking slightly back and forth when standing is necessary, and resting with the legs elevated.

See also HEMORRHOIDS; PLASTIC SURGERY; TELANGIECTASIS; WALKING FOR FITNESS; WEIGHT LOSS AND WEIGHT MANAGEMENT.

vein A blood vessel that carries BLOOD to the HEART. All veins except the PULMONARY VEINS carry deoxygenated blood; the pulmonary veins return oxygenated blood to the heart from the LUNGS. Because veins lack the muscular structure and contractile capability of arteries, they have valves that keep blood moving only in one direction, toward the heart. The body's largest veins are the superior VENA CAVA and the inferior vena cava, which empty blood into the heart's right atrium.

For further discussion of the veins within the context of cardiovascular structure and function please see the overview section "The Cardiovascular System."

See also ARTERY.

vena cava The body's largest veins, which return deoxygenated BLOOD to the HEART. The superior vena cava brings blood from the upper body and enters the top of the right atrium. The inferior vena cava brings blood from the lower body and enters the bottom of the right atrium. A valve at the juncture of the inferior vena cava and the right atrium, called the eustachian valve, prevents gravity from pulling blood back into the inferior vena cava.

For further discussion of the superior vena cava and the inferior vena cava within the context of cardiovascular structure and function please see the overview section "The Cardiovascular System."

See also AORTA; PULMONARY ARTERIES; PULMONARY VEINS.

venous insufficiency A chronic condition in which the veins cannot adequately return BLOOD to the HEART, usually as a consequence of defective valves that allow blood to leak back and pool in the veins. Some people do not have valves in their veins, a circumstance that is a CONGENITAL ANOMALY. Venous insufficiency primarily affects the veins in the legs, especially the lower legs, and may accompany or contribute to VARICOSE VEINS. Symptoms include edema and characteristic changes in SKIN color and texture (lipodermatosclerosis). Many people who have venous insufficiency experience discomfort, such as burning or itching, and cramping in the lower legs, and may have frequent skin ulcers that are slow to heal. The diagnostic path may include Doppler ULTRASOUND or VENOGRAM to evaluate the flow of blood through the veins.

Treatment is conservative and supportive to the extent possible, including compression stockings to help support the veins and intensify the action of the leg muscles with walking. Frequent walking massages the veins, helping move blood upward toward the heart. Resting with the legs elevated above the level of the heart counters the effect of gravity on returning blood flow. Surgery may become necessary when skin ulcers fail to heal with treatment, or PAIN becomes intense. Surgical options include VEIN ligation (commonly called vein stripping) and vein grafts to reroute blood around severely damaged veins.

See also DEEP VEIN THROMBOSIS (DVT).

venogram A diagnostic procedure to evaluate the flow of blood in the veins, usually in the legs.

The cardiologist may use venogram to diagnose VARICOSE VEINS, VENOUS INSUFFICIENCY, or DEEP VEIN THROMBOSIS (DVT). For venogram, the radiologist injects a small amount of contrast dye into the affected VEIN network and then takes X-rays or fluoroscopy images as the dye moves with the blood through the veins. The venogram shows any structural abnormalities and occlusions. Venogram requires no preparation or recovery. Some people experience a minor burning sensation with injection of the contrast dye. People who are allergic to iodine may have an allergic reaction to the dye.

See also ULTRASOUND; X-RAY.

ventricular assist devices (VADs) Implanted mechanical pumps that aid the native HEART, taking over some of the workload of the ventricles. Several types of VADs are available, each with somewhat different features and functions. A VAD may assist the right or left ventricle, and in some cases both ventricles, as a bridge device while awaiting a donor heart for HEART TRANSPLANTATION or as a permanent device to treat end-stage HEART FAILURE, a therapeutic application sometimes called destination therapy. The VAD sometimes allows the heart to recover sufficiently that the VAD becomes unnecessary and the surgeon can remove it. The OPEN HEART SURGERY to implant the VAD takes between three and eight hours, depending on the person's cardiovascular status and the type of VAD the surgeon is implanting.

Though VADs offer hope of extended survival and improved QUALITY OF LIFE for many people whose heart failure would otherwise be fatal, living with an implanted device requires conscientious and consistent attentiveness. Recipients must take anticoagulant medications and may require other medications, depending on their underlying CARDIOVASCULAR DISEASE (CVD). Ongoing risks include INFECTION, mechanical failure of the VAD, damage to blood cells, bleeding at the implant site, clot formation resulting in STROKE or PULMONARY EMBOLISM, and worsening of cardiovascular status that may require additional therapeutic intervention including surgery. Because the VAD became an approved treatment in the United States only in 2004, doctors do not yet know the long-term benefits and risks of VAD implantation.

See also LIVING WITH CARDIOVASCULAR DISEASE; MEDICATIONS TO TREAT CARDIOVASCULAR DISEASE; ORGAN TRANSPLANTATION.

ventricular fibrillation Rapid, irregular, ineffective contractions of the heart's ventricles. Ventricular fibrillation quickly becomes fatal without treatment. The HEART cannot pump blood to the LUNGS or to the body when it is in ventricular fibrillation.

Ventricular fibrillation is a life-threatening event that requires emergency medical treatment.

The ELECTROCARDIOGRAM (ECG) provides a definitive diagnosis. Treatment may consist of DEFIBRILLATION (an electrical shock to the heart) or of medications to restore normal rhythm. Ventricular fibrillation typically follows a cardiac crisis such as HEART ATTACK, and despite its lethal potential presents an opportunity for successful resuscitation because the heart still has electrical activity. Ventricular fibrillation may also exist as the deterioration of an ARRHYTHMIA disorder such as ventricular tachycardia (rapid, regular contractions of the ventricles) or WOLFF-PARKINSON-WHITE SYNDROME.

See also ATRIAL FIBRILLATION; CARDIOPULMONARY RESUSCITATION (CPR); PREMATURE VENTRICULAR CONTRACTION (PVC).

Wolff-Parkinson-White syndrome An inherited ARRHYTHMIA disorder in which an extra conduction pathway, called an accessory pathway, exists between the heart's atria and ventricles. The accessory pathway allows the heart's electrical pacing impulse to bypass the normal conductive route, reaching the ventricles before the atria have completed their contraction cycle. While many people who have Wolff-Parkinson-White syndrome never experience any symptoms, some people have episodes of ventricular tachycardia, in which the ventricles contract regularly though very rapidly. Ventricular tachycardia is not very effective in moving BLOOD to the LUNGS and especially through body, resulting in feelings of lightheadedness or episodes of SYNCOPE (brief loss of CONSCIOUSNESS) as the blood supply to the BRAIN becomes diminished.

The ELECTROCARDIOGRAM (ECG) provides the diagnosis, showing the accessory conductive pathway. People who do not have symptoms do not need treatment though should receive regular follow-up evaluation from a cardiologist. When symptoms are present, treatment is necessary and may take the form of medication to regulate the heart's rhythm or RADIOFREQUENCY ABLATION to destroy the extra pathway. Wolff-Parkinson-White syndrome tends to show symptoms in early to middle adulthood. Undetected and untreated Wolff-Parkinson-White syndrome may result in SUDDEN CARDIAC DEATH. With appropriate treatment, most people who have the condition no longer experience symptoms.

See also CARDIAC CYCLE; HEART; LONG QT SYNDROME (LQTS); MEDICATIONS TO TREAT CARDIOVASCULAR DISEASE.

THE BLOOD AND LYMPH

The BLOOD and LYMPH are the cell-bearing fluids that nourish and protect the body. Physician specialists who treat conditions of the blood and lymph are hematologists. This section, "The Blood and Lymph," presents an overview of the structures and functions of the blood and lymph, a discussion of hematologic and lymphatic health and disorders, and entries about the health conditions that can affect the blood and lymph.

Structures of the Blood

BLOOD
PLASMA
BONE MARROW
erythrocytes
  reticulocytes
platelets (thrombocytes)
leukocytes
  lymphocytes:
   B-cells, T-cells
  monocytes
  granulocytes:
   basophils,
   eosinophils, neutrophils
SPLEEN
THYMUS
LYMPH
LYMPH NODES
  cervical nodes
  axillary nodes
  epitrochlear nodes
  inguinal nodes
LYMPH VESSELS
  CISTERNA CHYLI
  THORACIC DUCT
  RIGHT LYMPHATIC DUCT

Functions of the Blood and Lymph

The BLOOD and the LYMPH are the body's vital fluids, sharing responsibility for nourishment, cleansing, IMMUNE RESPONSE, and fluid balance. The blood primarily nourishes the cells, and the lymph cleanses and drains the tissues. The lymph derives from as well as returns to the blood. Though the blood and the lymph are unique fluids that circulate through separate networks, they share some structures that allow leukocytes, notably lymphocytes and granulocytes, to move freely between the blood and the lymph.

The rhythm of life: the blood The adult human body contains about five liters (just under six quarts) of blood that the HEART propels on a continuous circuit through the arteries and veins. Contained within the arteries and veins of the pressurized cardiovascular system, the total blood volume circulates from the heart, through the body, and back to the heart in about a minute. During strenuous activity the blood can pound through six full circuits in a minute, hammering oxygen and GLUCOSE to the cells to fuel their increased energy output.

Though fluid the blood is a living tissue, a mix of cells (45 percent of the blood's composition) suspended in a watery matrix of PLASMA (55 percent of the blood's composition). Plasma, which is about 90 percent water, also carries numerous substances dissolved in it including electrolytes, glucose (sugar), hormones, NUTRIENTS, and proteins such as CLOTTING FACTORS and ALBUMIN. A single drop of blood contains roughly:

- 500 million erythrocytes
- 33.5 million platelets
- 830,500 leukocytes

Blood cell production: the bone marrow The red BONE MARROW, located in cavities within the bones called medullary canals, produces 99 percent of the adult body's blood cells and all of its erythrocytes. This spongy, somewhat gelatinous substance has two structures, the vascular compartments through which blood circulates and the extravascular compartments that contain the BLOOD STEM CELLS. The red bone marrow is extraordinarily active tissue, releasing into circulation 2 to 3 billion erythrocytes, 2 to 3 billion platelets, up to 100 billion granulocytes, and several hundred million monocytes every 24 hours. The BONE

marrow also warehouses minerals it requires for cell synthesis and the bones need for STRENGTH and growth, such as calcium. As well, the bone marrow stores B-cell lymphocytes and plasma cells, leukocytes integral to the body's IMMUNE RESPONSE.

Oxygen transport: erythrocytes The erythrocytes, also called red blood cells (RBCs), pick up oxygen molecules in the LUNGS and carry them to the cells. After delivering the oxygen, the erythrocytes then retrieve carbon dioxide molecules, the waste byproducts of cellular METABOLISM, and cart them back to the lungs for elimination from the body through respiration. This OXYGEN–CARBON DIOXIDE EXCHANGE is the foundation of the body's survival. No cells in the body can survive longer than 10 to 15 minutes (three to five minutes for BRAIN and heart cells) without oxygen.

Erythrocytes acquire their capacity to carry oxygen from the pigmented protein HEMOGLOBIN, which is high in iron. The pigment also gives erythrocytes their red color. The iron hemoglobin contains allows the hemoglobin to bind with the oxygen molecules. A healthy, normal erythrocyte contains about 300 million molecules of hemoglobin; each molecule of hemoglobin can bind with four molecules of oxygen. Iron enters the body from dietary sources. Iron deficiency is the most common cause of ANEMIA, a condition in which the blood cannot meet the body's oxygenation needs.

Erythrocytes are concave on both sides, giving them the FLEXIBILITY to nearly fold in half to squeeze through the narrowest of the body's blood vessels, the arterioles, venules, and capillaries. As well, erythrocytes lack nuclei, the "command" structures common to cells that contain deoxyribonucleic acid (DNA). DNA gives the cell its replication instructions; without it a cell cannot reproduce. The absence of a nucleus further aids the erythrocyte's flexibility, however, which is most important for delivering oxygen deep within the body's tissues.

Because erythrocytes cannot proliferate, the red bone marrow churns out a steady supply of new ones, releasing them into the circulation at a rate of 2 to 3 million per second. Erythrocytes enter the bloodstream in a slightly immature stage, called reticulocytes. They reach full maturity after about 24 hours in circulation and live in the bloodstream for 110 to 120 days, after which the SPLEEN filters them from the blood and breaks them down (hemolyzes) into their component structures. The LIVER further metabolizes the components of hemolyzed erythrocytes, recycling their ingredients for use in synthesizing new erythrocytes as well as to manufacture BILE and other biochemical substances. Macrophages within the liver, migratory monocytes called Kupffer cells, then consume whatever remains of the erythrocytic waste.

Stop the bleeding: platelets The smallest cell elements in the blood, platelets, are encased in protein coatings that become adhesive (sticky) when chemical messengers released at the site of bleeding enter the bloodstream. The chemicals activate PLATELET AGGREGATION, in which platelets swarm to the site of bleeding and stick to each other as well as to the collagen fibers at the site to form a hemostatic plug. This activation also enables platelets to change shape, elongating or contracting as necessary to bridge the gaps among the collagen fibers to form a weblike structure that ensnares other cells and substances. As the coagulation cascade unfolds the plug expands and hardens, eventually forming the clot that halts the bleeding. On the surface of the SKIN, this clot is a scab. Within a blood vessel, it is a thrombus.

Platelets arise from the largest cells in the red bone marrow, megakaryocytes, and actually are fragments of megakaryocytic cytoplasm rather than independent cells. They are irregularly shaped and loosely defined, a structure ideally suited to their purpose. Platelets also lack nuclei and live in the circulation for about 10 days. Roughly a third of the body's total platelet volume resides in the spleen, which releases them into the circulating blood in response to bleeding.

Defend and protect: leukocytes The leukocytes, also called white blood cells (WBCs), are the foundation of the body's IMMUNE RESPONSE. They take one of three forms: LYMPHOCYTE, MONOCYTE, or GRANULOCYTE. Each has specialized functions within the immune response. Lymphocytes attack invading pathogens, and monocytes and granulocytes consume the remains of the pathogenic invaders. Lymphocytes circulate primarily in the lymph. Monocytes circulate in the blood for about 24 hours after the bone marrow releases them and

then migrate into the tissues where they establish themselves as fixed defenders called macrophages. Granulocytes circulate in the blood and in the lymph and also take up residence in the lymph structures and the general body tissues. The three subtypes of granulocytes—basophils, eosinophils, and neutrophils—have specified roles in the body's inflammatory response and are responsible for hypersensitivity reactions and allergies. The bone marrow primarily manufactures leukocytes, with assistance from the lymph tissues and spleen when necessary to meet the body's INFECTION control needs.

Flow with the body: the lymph In contrast to the force of the blood's circulation, the lymph channels through the body at a gentle flow of about 100 milliliters per hour. Gravity and the body's movements (MUSCLE contractions) massage lymph through the lymph vessels that roughly parallel the arteries and veins. The lymph vessels are thin-walled, originating with cul-de-sac structures arising in the epithelial spaces, the lymphatic capillaries, that join increasingly larger channels that carry lymph into the central body and ultimately into the circulating blood.

Slightly more watery than blood (92 percent), lymph carries a suspension of primarily lymphocytes and monocytes as well as dissolved proteins and other substances. Clear and only slightly more viscous than water, lymph drains from the spaces between cells into the lymphatic capillaries, microscopic channels comprised of a single thickness of cells overlapped like backward shingles. This construction encourages fluid to seep under the cells and into the lymph capillaries. The lymph capillaries collect the droplets of lymph, pooling them into microscopic trickles that eventually merge with larger lymphatic vessels—the CISTERNA CHYLI, THORACIC DUCT, and RIGHT LYMPHATIC DUCT—that carry the lymph toward the subclavian veins where it rejoins the bloodstream.

The lymph carries leukocytes, proteins, antibodies, and other materials directly to the cells. While erythrocytes in the blood can carry oxygen molecules into the CAPILLARY BEDS, the capillaries eventually become too narrow even for the flexible erythrocytes to make further passage. So the erythrocytes off-load their oxygen molecules into the lymph, which floats them through the capillary walls and into the interstitial spaces (the space between the cells of the tissues). Lymph flows through the interstitial spaces, bathing the cells, which then withdraw the nutrients, including oxygen and glucose, that they require. Cells also discharge their metabolic wastes into the lymph.

Critical passengers in the lymph are the leukocytes, predominantly neutrophils and lymphocytes. These protective cells vigilantly patrol the interstitial spaces on the alert for invading pathogens. When they detect pathogenic invaders leukocytes secrete chemicals, called CYTOKINES, into the lymph that initiate or activate specific immune responses. Some of these responses recruit additional lymphocytes and granulocytes (notably neutrophils) into circulation both in the lymph and in the blood. As agents of immune response, granulocytes and lymphocytes have the ability to migrate between the blood and the tissues, bolstering the body's defenses as needed.

The lymph also transports pathogens, such as viruses and bacteria, to the lymph nodes where masses of lymphocytes, macrophages (tissue-bound monocytes), and granulocytes wait to dispose of them. The lymph nodes often swell when they are busy fighting infections (LYMPHADENOPATHY) and may themselves become infected (LYMPHADENITIS). The lymph also offers a route of transport for cancer cells that leave the original tumor site. The lymph network can unfortunately carry cancer cells that enter its flow to any location within the body, facilitating METASTASIS (spread of the cancer).

Teaching the concept of self: the thymus The thymus, a loose structure of lymph tissue behind the sternum (breastbone) in the center of the chest, functions somewhat as a prep school for immature T-cells. In the thymus, T-cells learn to distinguish between "self" and "nonself," a fundamental concept of immune function that prevents the IMMUNE SYSTEM from attacking cells that belong to the body. The thymus releases those that learn the lesson, and they migrate into the lymph tissues where they can reside for many years. T-cells that fail to recognize self and nonself do not gain release, and they die without leaving the thymus. In AUTOIMMUNE DISORDERS such as MYASTHENIA GRAVIS and SYSTEMIC LUPUS ERYTHEMATOSUS (SLE), it

appears the education of T-cells somehow goes awry, and the thymus releases those that identify certain self cells as nonself. These misguided T cells attack the mistaken self cells as though they were nonself, causing an autoimmune (self-attack) response.

The thymus is most active in childhood, reaching its peak function and size in early ADOLESCENCE. By early adulthood the thymus shrinks to a mere fibrous shadow of its most proliferative self. In the 1940s doctors erroneously drew a correlation between the normally large thymus of childhood and what subsequently became known as SUDDEN INFANT DEATH SYNDROME (SIDS), resulting in "therapeutic" irradiation of the thymus to reduce its size. Unfortunately, this permanently crippled the immune system, an often fatal consequence in a time when antibiotic therapy was in its infancy. Though even today researchers do not fully understand the role of the thymus in adulthood, they know it secretes a number of hormones that appear to have functions related to immune response. THYMECTOMY (surgery to remove the thymus) remains a therapeutic option in very limited circumstances, such as in adults who have myasthenia gravis.

Health and Disorders of the Blood

The blood often is the first location within the body where health conditions manifest, and as well is itself vulnerable to disorders that affect its ability to function. Even conditions that do not directly affect the blood's function show up in the blood, such as DIABETES (elevated blood glucose levels) and ATHEROSCLEROSIS (elevated blood lipids). Diagnostic blood tests, notably the complete blood count (CBC), are part of most clinical evaluations. The numbers, types, and cytologic details of the blood cells provide crucial clues to doctors investigating broad-ranging symptoms such as fatigue, chronic infection, or allergies.

Anemia, an inability of the blood to meet the body's oxygenation needs that affects about 3.5 million people in the United States, results from numerous and varied health circumstances and conditions. SICKLE CELL DISEASE and THALASSEMIA are GENETIC DISORDERS that result in defective erythrocytes. LEUKEMIA, lymphoma, and MULTIPLE MYELOMA are cancers that involve the blood cells and the structures that make them. Inherited deficiencies alter specific aspects of the blood's composition and function, such as HEMOPHILIA, a deficiency of clotting factors that results in excessive bleeding. In many situations treating the underlying health condition eliminates its effect on the blood, such as with many types of anemia. In other cases, such as leukemia, treatment targets the blood or blood-producing organs and structures.

CONDITIONS THAT INVOLVE THE BLOOD AND THE LYMPH

ANEMIA	DISSEMINATED INTRAVASCULAR COAGULATION (DIC)
hemangioma	HEMOCHROMATOSIS
HEMOPHILIA	LEUKEMIA
LEUKOPENIA	LYMPHADENITIS
LYMPHEDEMA	lymphocytopenia
lymphoma	methemoglobinemia
MULTIPLE MYELOMA	MYELODYSPLASIA SYNDROME
MYELOFIBROSIS	NEUTROPENIA
POLYCYTHEMIA VERA	THALASSEMIA
THROMBOCYTHEMIA	THROMBOCYTOPENIA
thrombophilia	thrombosis
VON WILLEBRAND'S DISEASE	

Traditions in Medical History

Though ancient healers understood the importance of blood to health and to life itself, they did not understand the mechanisms of its circulation or production. Doctors did not know these details of physiology until the 17th and 18th centuries, respectively. The great GALEN (129–199), father of Western medicine, pronounced that the liver was the source of the body's blood, constantly producing this vital fluid much as a natural spring produced water, with an equal mix of regularity and mystery. Though centuries later researchers would discover the fragment of truth in this view—the liver does indeed produce the cells of the blood early in fetal development—its fallacy nurtured peculiar medical practices throughout much of modern history. Among the most persistent was that of bloodletting, which remained a mainstay of clinical practice into the 20th century as a treatment for nearly any condition that did not respond to other therapeutic methods. Modern doctors know, of course, that bloodletting drains the body of the cells it needs most to fight infection.

MODERN THERAPEUTIC BLOODLETTING

As was the case with Galen's views on the source of BLOOD, there is also a fragment of validity in the practice of bloodletting. Contemporary physicians use modern variations of this ancient practice to treat several conditions. Therapeutic PHLEBOTOMY withdraws blood to treat HEMOCHROMATOSIS, in which the blood contains too much iron. Therapeutic HEMAPHERESIS selectively extracts components of the blood and returns the remainder to the individual, such as to treat SICKLE CELL DISEASE.

In 1628 British physician William Harvey (1578–1657) refuted Galen's pronouncement with his published evidence of the blood's circulation through a closed network of arteries and veins, establishing the recognition of the blood as a finite composition within the body. Within 20 years physicians began experimenting with BLOOD TRANSFUSION, though what was to become a lifesaving mainstay of medical treatment did not become practical until the early 1900s. Karl Landsteiner (1868–1943), an Austrian-American immunologist, was the first researcher to identify the polysaccharides on the surface of erythrocytes (red blood cells) that were to become known as blood types. The discovery at last explained why one person's blood could harm another person and made possible the therapeutic use of drawing blood from one person for transfusion into another person. Landsteiner won the 1930 Nobel Prize in medicine or physiology for his work, and by the 1950s blood transfusions were standard therapy for a wide range of health conditions.

Transfused blood became a notorious vehicle of death in the early 1980s with the eruption of HIV/AIDS in Western populations. Though scientists had long known of blood's ability to transmit infections such as MALARIA and HEPATITIS, this new VIRUS became a particularly lethal threat for people who relied on chronic blood transfusions to treat health conditions such as hemophilia and sickle cell anemia. It also raised ethical dilemmas in situations of massive trauma in which the only treatment was equally massive transfusions of blood. Thousands of people acquired HIV/AIDS from blood and blood products until reliable screening procedures and testing for the presence of HIV in donor blood became available in the late 1990s.

Breakthrough Research and Treatment Advances

Among the most significant breakthroughs in treatment advances are therapies for cancers of the blood, bone marrow, and lymphatic tissues. Complex CHEMOTHERAPY regimens, bone marrow transplantation, and peripheral blood stem cell (PBSC) transplantation can turn some leukemias from fatal to long-term REMISSION or cure. About 80 percent of children under age 14 who undergo treatment for acute lymphatic leukemia (ALL), for example, experience complete and apparently permanent remission such that doctors are willing to call them cured.

Much current research centers on blood stem cells, with scientists searching for ways to encourage these pluripotent cells to differentiate into cells of types other than blood cells. Peripheral blood stem cells share many of the characteristics of their omnipotent counterparts, embryonic STEM CELLS, including the ability to either replicate themselves or differentiate into specific cell types, and are easy to collect via extraction from BLOOD DONATION or HEMAPHERESIS. Though these efforts have so far met with limited success, they have resulted in new understanding of the complexities that underlie cell differentiation and proliferation in both health and disease.

A

aging, changes in the blood and lymph that occur with The BLOOD undergoes a number of normal changes across the span of the lifetime. Blood cells have life spans ranging from a few hours to decades. The blood continually renews itself, producing millions of erythrocytes and thousands of leukocytes every hour. Blood cell production accelerates to meet unique health needs, such as PREGNANCY or INFECTION.

The LIVER is the first organ in the developing fetus to produce blood cells, primarily erythrocytes, with supplemental production from the SPLEEN and the THYMUS. At about five gestational months the BONE MARROW has developed enough to begin taking over blood cell production and by birth is the primary structure for HEMATOPOIESIS. Through childhood (until about age 16), nearly all the bone marrow is red bone marrow that actively produces blood cells. As the body matures yellow bone marrow, a fibrous structure of connective tissue and fat, gradually replaces the red bone marrow. By adulthood only about 60 percent of the bone marrow is red. This level remains fairly constant until around age 70, when some red bone marrow, primarily in the long bones, again transitions to yellow marrow.

The bone marrow slows ERYTHROCYTE (red blood cell) production in advanced age, putting fewer erythrocytes into the blood's circulation. The reduced erythrocyte volume correspondingly decreases the amount of available HEMOGLOBIN in the blood, which diminishes the amount of oxygen the blood can carry to the cells with each heartbeat. This reduction commonly results in decreased AEROBIC CAPACITY, showing lessened ENDURANCE and longer recovery times with strenuous physical activity, and may cause ANEMIA. The spleen's efficiency at removing old and defective erythrocytes from the circulation declines, an accommodation that is somewhat a double-edged sword. While this slowed hemolytic action allows more erythrocytes to remain in the blood to improve the blood's capacity to carry oxygen, a greater number of those erythrocytes are less effective in this role.

The LYMPH structures and functions also change with age. The lymphatic system becomes active at about age two months when the child's IMMUNE SYSTEM begins to replace the protection from the mother's IMMUNITY. Most of the lymphocytes the lymph tissues produce swarm to the THYMUS, where they will come to maturity. The thymus contains nearly the lifetime complement of immature T-cell lymphocytes (called thymocytes in immaturity) by about age 16, at which point the thymus reaches its peak size and level of function. As the T-cells reach maturity they leave the thymus and migrate to other lymph structures throughout the body where they reside until the immune system needs them. As T-cell maturation winds down the activity of the thymus decreases and the thymus begins to shrink, diminishing by early adulthood to a few clusters of lymph tissue. After adulthood, the body can make only limited additional T-cells. Health conditions that affect T-cells, such as HIV/AIDS, that destroys them can deplete the body's supply of these vital protective cells, depriving the body of its front line immune defense.

With age lymphocyte production also decreases, resulting in fewer circulating lymphocytes and a corresponding reduced resistance to infection. Later in life the spleen diminishes in size, ultimately retreating to about half its size in early adulthood. Its functional capacity decreases as well, resulting in the spleen becoming less efficient at filtering

aged erythrocytes from circulation. The spleen also becomes less effective in fighting infection, reducing the body's resistance.

Other changes in the body that occur with advancing age affect the ability of the LYMPH VESSELS to collect fluid from the tissues and transport it back to the bloodstream. Diminished MUSCLE tone and reduced movement slow the flow of fluids into and through the lymph vessels. Other health conditions such as congestive HEART FAILURE and kidney disease affect the body's ability to move fluids through the blood vessels, creating a backlog. By about age 70, however, the body begins to decrease the total amount of water its tissues retain. This results in less water in the blood and a lower blood volume, somewhat lowering the BLOOD PRESSURE though increasing the risk for blood clots (thrombosis).

See also AGING, CARDIOVASCULAR CHANGES THAT OCCUR WITH; AGING, PULMONARY CHANGES THAT OCCUR WITH; CANCER RISK FACTORS; SENESCENCE.

albumin The most abundant protein in PLASMA. Albumin transports various molecules through the BLOOD and helps sustain the blood's oncotic pressure, keeping fluid from seeping into the tissues. Albumin molecules are larger than the molecules it transports, allowing those substances, such as electrolytes and hormones, to pass through the walls of the blood vessels while the albumin molecules remain within the blood vessels. Albumin is among the numerous plasma proteins the LIVER produces. Albumin is also available as a blood product for transfusion. Blood banks obtain it by separating it, using a cell separator, from donated whole blood or plasma.

The blood of a healthy adult contains 3.5 to 5.0 grams per deciliter (g/dL) of albumin, which makes up about 2 percent of the blood's total volume. A low serum albumin level (hypoalbuminemia, decreased concentration of albumin in the blood) often indicates liver disease such as CIRRHOSIS or kidney disease such as GLOMERULONEPHRITIS. Hypoalbuminemia also occurs with serious BURNS. An elevated albumin level (hyperalbuminemia, increased concentration of albumin in the blood) occurs less commonly and often signals extended DEHYDRATION or DIABETES INSIPIDUS, a disorder of the ADRENAL GLANDS.

See also AGING, CHANGES IN THE BLOOD AND LYMPH THAT OCCUR WITH; BLOOD PRESSURE; BLOOD TRANSFUSION.

anemia A reduced ability of the BLOOD to meet the body's oxygenation needs arising from either a diminished volume of erythrocytes (red blood cells) in the blood or from reduced HEMOGLOBIN content in the erythrocytes. Though the common perception of anemia is that it is itself a health condition, doctors consider anemia an indication of other health conditions. Diagnosis and treatment target those underlying conditions. Anemia affects about 3.5 million people in the United States. Anemia can affect people of any age though is most common among menstruating women and during PREGNANCY.

Causes of Anemia

Anemia may be acute (come on suddenly) or chronic (continue over an extended time). Anemia may also result from medication interactions or ADVERSE REACTIONS, CHEMOTHERAPY, RADIATION THERAPY, and numerous health conditions. In general, anemia results from three circumstances, individually or in combination:

- excessive blood loss drains erythrocytes from the body
- the SPLEEN destroys (hemolyzes) too many erythrocytes
- the BONE MARROW produces too few defective erythrocytes

Blood loss Blood loss, either in large quantity suddenly or through chronic bleeding, has a twofold consequence on the blood's ability to carry oxygen. First, the bleeding reduces the number of erythrocytes in the blood, making fewer erythrocytes and thus less hemoglobin available. Second, old erythrocytes, which the spleen culls from the circulation to dismantle and recycle, are a key source of ingredients such as iron and hemoglobin for the production of new erythrocytes. Traumatic hemorrhage, GASTROINTESTINAL BLEEDING, and heavy menstrual bleeding are among the causes of anemia related to blood loss.

Erythrocyte destruction or deformity One of the spleen's roles is to filter erythrocytes from the blood that are old or defective, a normal process called HEMOLYSIS that maintains an appropriate balance of erythrocytes in the blood. The spleen may inappropriately sequester and destroy healthy erythrocytes, sometimes without apparent reason. SICKLE CELL DISEASE is a complex genetic disorder that results in malformed erythrocytes, causing anemia among other symptoms. In THALASSEMIA, another genetic disorder, erythrocytes are normal but hemoglobin is defective.

Inadequate erythropoiesis Nutritional deficiencies and renal failure are the leading causes of diminished erythropoiesis. The bone marrow requires vitamin B_{12}, iron, and folic acid to manufacture erythrocytes. Pernicious anemia results when the STOMACH fails to produce intrinsic factor, a substance necessary to absorb vitamin B_{12} from ingested foods. When these vital NUTRIENTS are lacking, the bone marrow cannot generate new erythrocytes. Iron deficiency anemia is the most common type of anemia in the United States.

Kidney disease and RENAL FAILURE also affect erythropoiesis because the KIDNEYS secrete ERYTHROPOIETIN (EPO), the HORMONE that stimulates the bone marrow to produce erythrocytes. Bone marrow disorders such as myelofibrosis and MULTIPLE MYELOMA also disturb HEMATOPOIESIS. Aplastic anemia is a life-threatening type of anemia that results when the bone marrow completely shuts down blood cell production.

COMMON CAUSES OF ANEMIA

adverse DRUG reactions	CHEMOTHERAPY
chronic HEPATITIS	CIRRHOSIS
DYSMENORRHEA	environmental toxins
folic acid deficiency	GALLBLADDER DISEASE
GASTROINTESTINAL BLEEDING	HEMOLYSIS
hemorrhage	HIV/AIDS
INFLAMMATORY BOWEL DISEASE (IBD)	iron deficiency
LEUKEMIA	lymphoma
MALABSORPTION syndromes	MULTIPLE MYELOMA
MYELODYSPLASIA SYNDROME	MYELOFIBROSIS
PREGNANCY	RADIATION THERAPY
RENAL FAILURE	SICKLE CELL DISEASE
SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)	THALASSEMIA
vitamin B_{12} deficiency	

Symptoms and Diagnostic Path

Many people do not have symptoms of anemia but instead find out they have anemia through blood tests conducted for other reasons, such as during ROUTINE MEDICAL EXAMINATION or screening for BLOOD DONATION. When symptoms are present, they are generally the same regardless of the underlying cause and commonly include

- tiredness and fatigue
- breathlessness, especially with physical exercise
- HEADACHE
- chronically cold or tingling hands and feet
- PALPITATIONS or ARRHYTHMIA (irregular or rapid heartbeat)
- irritability
- paleness of the SKIN, nail beds, and gums

Hemolytic anemia may also cause JAUNDICE. Severe anemia can be debilitating, preventing an individual from participating even in everyday activities. Such severe anemias generally result from serious underlying health circumstances. Diagnostic blood tests including complete blood count (CBC), hemoglobin, and hematocrit often provide the initial diagnosis. Further tests might include bone marrow biopsy to determine whether the bone marrow is adequately producing erythrocytes or whether the erythrocytes are normal. The doctor may choose to perform other diagnostic procedures, depending on the findings. Whether or not the anemia causes symptoms, it is important to find its cause.

Treatment Options and Outlook

Most types of anemia are curable or treatable. Treatment targets the underlying cause of the anemia. Supplemental iron, vitamin B_{12}, and folic acid can improve many types of anemia. Pernicious anemia requires lifetime injections of vitamin B_{12}. Aplastic anemia or anemia due to chronic health conditions may require BLOOD TRANSFUSION or BONE MARROW TRANSPLANTATION. Doctors may treat chronic anemia or transient anemia due to cancer treatment with EPO supplementation. Anemia resulting from GENETIC DISORDERS such as sickle cell disease or thalassemia requires ongoing treatment. Successful treatment of the

underlying cause nearly always eliminates the anemia. Most anemias are curable or treatable.

Risk Factors and Preventive Measures

A number of factors can create risk for developing anemia. People who are at greatest risk for anemia are those who

- consume a diet low in iron, folic acid, and vitamin B_{12}, nutrients the bone marrow requires to manufacture erythrocytes
- have gastrointestinal conditions that interfere with nutrient absorption, notably INFLAMMATORY BOWEL DISEASE (IBD), MALABSORPTION disorders, and CELIAC DISEASE
- menstruate or are pregnant
- have chronic health conditions that strain the body's resources, such as AUTOIMMUNE DISORDERS or INFECTION (for example, HEPATITIS or HIV/AIDS)
- have blood disorders; LEUKEMIA, LYMPHOMA, or multiple myeloma; or who are undergoing CHEMOTHERAPY or RADIATION THERAPY for other types of CANCER

People at risk for anemia should have their blood tested regularly and any time they develop symptoms of anemia. Though it is not always possible to prevent anemia, early treatment can minimize the adverse effects of anemia on overall health as well as intervene in the underlying condition at an early stage.

See also DISSEMINATED INTRAVASCULAR COAGULATION (DIC); HEMATOPOIESIS.

apheresis See HEMAPHERESIS.

B

basophil See GRANULOCYTE.

blood The cell-filled fluid that carries vital chemicals and NUTRIENTS via the cardiovascular system to tissues and cells throughout the body. The HEART pumps the blood, sending it under pressure through a closed network of arteries and veins. The blood provides volume within the cardiovascular system, establishing both BLOOD PRESSURE and osmotic pressure (the pressure that keeps fluid within the blood vessels). The blood carries oxygen and nourishment to and collects metabolic wastes from the cells. The blood also serves as the body's primary IMMUNE RESPONSE mechanism, transporting antibodies and specialized cells that defend the body from INFECTION as well as aid in HEALING wounds. The blood's basic composition is about 55 percent PLASMA (liquid) and 45 percent cells. The adult human body contains about five liters, or five and a half quarts, of blood accounting for 8 percent of total body weight.

Plasma

Plasma is 90 percent water. It contains a mix of proteins, electrolytes, hormones, antibodies, minerals, GLUCOSE, and other dissolved substances, forming a solution in which the blood's cells float. The constant churning and movement of the blood as the heart pumps it through the blood vessels keeps the cells and the plasma well mixed. However, in a collected blood sample the cells quickly settle to the bottom, leaving the plasma at the top. The primary proteins in plasma are ALBUMIN, IMMUNOGLOBULIN, and CLOTTING FACTORS. Plasma has a higher concentration of electrolytes (salts) than fluid in the tissues, giving the blood a higher osmotic pressure that draws fluid into the blood rather than allows it to seep from the blood in the CAPILLARY BEDS. Plasma is also essential for COAGULATION (clotting) as it carries both clotting factors and the enzymes that activate them.

Blood Cells

The blood contains three kinds of cells:

- erythrocytes, or red blood cells, which carry oxygen from the LUNGS to every other cell in the body
- leukocytes, or white blood cells, which fight infection and take one of three forms: MONOCYTE, LYMPHOCYTE, or GRANULOCYTE
- platelets, also called thrombocytes, which cause blood to coagulate (clot)

Erythrocytes make up nearly the entire volume of blood cells, while leukocytes and platelets combined make up less than 1 percent. The red BONE MARROW synthesizes (produces) the vast majority of blood cells, a process called HEMATOPOIESIS. Other structures, such as the SPLEEN, can produce limited numbers of blood cells when the body is in crisis. The LIVER and the spleen cleanse damaged, old, and deteriorating blood cells from the blood. The liver breaks erythrocytes into their chemical components, which the body then recycles to synthesize new erythrocytes in the bone marrow.

For further discussion of the blood within the context of blood and lymph structure and function please see the overview section "The Blood and Lymph."

See also BLOOD DONATION; BLOOD TRANSFUSION; LYMPH.

blood donation The procedure of withdrawing BLOOD to prepare and use for BLOOD TRANSFUSION. Volunteer donors provide all human blood and

blood products used for transfusions. According to the American Association of Blood Banks, 8 million Americans donate 15 million units of blood each year. Because blood banks separate the majority of donated blood into component blood products, one unit of donated whole blood can meet multiple needs.

The body replaces lost fluid volume (PLASMA) within 24 hours of donation, and erythrocytes (red blood cells) and other blood cells in six to eight weeks. A healthy adult may donate one unit of whole blood every eight weeks. There is no cost for donating blood, and there is very minimal risk. A person cannot contract HEPATITIS, HIV/AIDS, or other infectious diseases through the process of donating blood.

Donor Requirements

In the United States, individual states and blood banks establish regulations and procedures to determine donor eligibility. In general, a prospective donor must

- be 17 years of age or older
- pass a preliminary health screening that identifies potential health risks for the donor or for recipients of the donor's blood
- weigh 100 pounds or more

Health screening questions aim to reveal behaviors or practices that carry a risk for INFECTION with diseases such as hepatitis and HIV/AIDS. Such behaviors include intravenous DRUG use and sex with multiple partners. In 1998, US blood banks also began screening prospective donors for possible exposure to variant Creutzfeldt-Jakob disease (VCJD), the human illness resulting from bovine spongiform encephalopathy ("mad cow" disease). Numerous health conditions may preclude an individual from donating blood; blood banks refer to these exclusions as deferrals.

The Blood Donation Procedure

The total blood donation process takes about 45 minutes to an hour, about 20 minutes of which is the actual blood withdrawal (called PHLEBOTOMY). Once the prospective donor clears the health screening, he or she sits in a reclining chair to be comfortable for the donation process. The technician cleanses the inner arm at the elbow with an antiseptic and puts a tourniquet briefly around the upper arm to cause the veins to engorge. The technician then inserts a sterile needle, connected to collection tubing and bag, into one of the veins and releases the tourniquet.

The technician may ask the person to periodically squeeze an object to help move blood through the VEIN during collection. After blood fills the collection bag (one unit), the technician withdraws the needle and places pressure over the puncture site for several minutes to suppress any bleeding, then applies a bandage that should stay in place for two to four hours. The person moves to a resting area, usually to have a drink of juice or water and a snack, then may leave when he or she feels comfortable. The risks associated with donating blood are very minor and may include bleeding, bruising, or discomfort at the needle insertion site.

Donor Blood Distribution and Use

Most donated blood goes to centralized blood banks for distribution to hospitals, which administer it to anyone who needs it. Two exceptions are

- autologous donation (BLOOD AUTODONATION), in which an individual donates blood for his or her own transfusion such as for a planned major surgery
- directed donation, in which an individual asks that others donate blood on his or her behalf and specified use, such as following a major trauma or unanticipated major surgery

Blood banks generally cannot use blood not used for self-transfusion (autologous donation) or not administered to the intended recipient (directed donation) for general transfusions and must instead throw it away. Some blood banks screen and process autologous donations differently from general donations, making autologous donations unacceptable for general use. Other blood banks handle autologous and general donations the same and have procedures for donors to authorize, at the time of donation, other use of their blood under such circumstances to avoid unnecessary waste of such a valuable resource. Though blood banks screen and process directed

donations the same as general donations, many health experts are concerned that donors may not be forthcoming during the health screening process, raising the risk for the blood to carry pathogens. The tests blood banks run on each unit of donated blood may not detect the presence of certain infections, making accurate health screening essential.

See also BONE MARROW DONATION; CREUTZFELDT-JAKOB DISEASE (CJD); HEMOCHROMATOSIS; HEMAPHERESIS.

blood stem cells The parent cells from which all BLOOD cells arise. Blood stem cells are pluripotent or undifferentiated, which means they have the ability to become any of the three types of blood cells (erythrocytes, leukocytes, or platelets). Intricate biochemical interactions determine how the blood stem cell will differentiate (become a specific type of blood cell). Blood stem cells reside primarily in the BONE MARROW and the LYMPH tissues though some circulate in the blood.

Blood stem cell transplantation, with harvesting through BONE MARROW DONATION and peripheral blood stem cell (PBSC) donation, has become a cornerstone of treatment for cancers involving the bone marrow and blood, notably leukemias and lymphomas. Researchers are exploring ways to use blood stem cells in other ways. Unlike embryonic stem cells, which are omnipotent (can differentiate into any kind of cell), blood stem cells have limited capability to differentiate only into the various types of blood cells. However, the abundance and ease of collection of blood stem cells, which can be extracted from the blood, gives researchers hope that they may discover methods to manipulate blood stem cell differentiation to give rise to other kinds of cells.

See also BONE MARROW TRANSPLANTATION; CELL STRUCTURE AND FUNCTION; HEMATOPOIESIS.

blood transfusion A therapeutic procedure to administer BLOOD or blood products. Blood transfusions may be autologous (self-donated), when the timing of the need for blood permits planning, or allogeneic (volunteer donor). The transfusion of blood or blood products takes place intravenously, through a sterile needle inserted into a VEIN. Receiving a transfusion may take 10 to 20 minutes, depending on the blood product, condition of the recipient's veins, and the urgency with which the person needs the blood product. Frozen blood products are thawed, and most blood products are brought to body temperature, before administration.

BLOOD RECLAMATION DURING SURGERY

Many hospitals use BLOOD reclamation, also called blood collection, procedures to collect, cleanse, and return to the person during the OPERATION blood lost during a major surgery such as orthopedic, transplant, or OPEN HEART SURGERY. This practice reduces the need for blood transfusions.

Blood Type Compatibility

Though physicians attempted blood transfusions as early as the 17th century, many hazards and failures accompanied the procedure until researchers discovered blood types in the early 1900s. The techniques to allow consistent detection of BLOOD TYPE, called type and cross-match, finally became available in the 1950s. Doctors then were able to routinely match the blood type and rhesus (Rh) factor of donors to recipients and blood transfusions became a standard element of medical care. Transfusion of whole blood and cell-containing blood products such as red blood cells (erythrocytes) requires blood type compatibility between donor and recipient; transfusion of other blood products such as PLASMA, ALBUMIN, and CLOTTING FACTORS does not.

BLOOD PRODUCTS FOR TRANSFUSION

whole BLOOD	packed red blood cells
PLASMA	ALBUMIN
clotting factor VII	clotting factor IX
platelets	cryoprecipitated antihemophilic factor (AHF)
fibrinogen	
antithrombin III	anti-inhibitor coagulation complex (AICC)
IMMUNOGLOBULIN	
Rh immunoglobulin	alpha 1-proteinase inhibitor
granulocytes	

Transfusion Reaction

Blood type incompatibility, though uncommon in transfusion, can lead to reactions spanning the spectrum from mild to fatal. Comprehensive type

and cross-match procedures of donor and recipient blood types prevent most blood incompatibility, though situations of extreme urgency (in which thorough type and cross-match is not possible) and occasionally human error result in incidents in which a blood transfusion recipient receives blood that is incompatible with his or her blood type. As well, blood may contain antigens that conventional type and cross-match procedures do not detect. People who have health conditions (such as SICKLE CELL DISEASE, THROMBOCYTHEMIA, and HEMOPHILIA) that require frequent or numerous transfusions often develop antibodies to other antigens commonly present in blood, increasing their risk for transfusion reaction.

Symptoms of transfusion reaction develop within 24 hours of receiving blood, though often begin during the transfusion, and may include

- FEVER
- chills
- URTICARIA (hives)
- PAIN in the lower back
- generalized physical discomfort

Mild transfusion reactions resolve with minimal medical intervention, such as medications to relieve fever and discomfort. Moderate to severe transfusion reaction may require CORTICOSTEROID MEDICATIONS to thwart the body's IMMUNE RESPONSE. Rarely, transfusion reaction can progress to thromboembolism that blocks the flow of blood through key arteries, including in the LUNGS to cause PULMONARY EMBOLISM, and cardiovascular SHOCK. Such severe complications are potentially fatal and require emergency medical treatment for the specific complications.

Transfusion-Transmitted Infections

Despite comprehensive screening tests and procedures, blood-borne infections remain a risk of blood transfusions. Screening can detect pathogens and antibodies that indicate the presence of infection for a number of blood-borne health conditions including HIV/AIDS, HEPATITIS (HVA, HVB, HVC), and SYPHILIS. Screening tests are only marginally successful at detecting other infections such as CYTOMEGALOVIRUS (CMV) and human T-lymphotropic virus (HTLV). Other pathogens are able to escape detection, notably those responsible for west Nile virus, MALARIA, and CREUTZFELDT-JAKOB DISEASE (CJD) as well as various BACTERIA.

Nearly all infections involve a time gap, the infection's INCUBATION PERIOD, during which the INFECTION is present in the blood though has not yet caused symptoms or antibodies. The risk for transfusion-transmitted infections is highest for blood donated during this phase of infection. Some blood banks are using a technology called nucleic acid testing (NAT), also called nucleic acid amplification testing, that can detect a virus's genetic material in the blood. This allows detection of the infection before the IMMUNE SYSTEM develops antibodies, shortening the window of time during which the PATHOGEN is present and infectious but undetectable.

INFECTIONS THAT BLOOD PRODUCT TRANSFUSIONS CAN TRANSMIT

BABESIOSIS	CREUTZFELDT-JAKOB DISEASE (CJD)
CYTOMEGALOVIRUS (CMV)	HEPATITIS A (HVA)
hepatitis B (HVB)	hepatitis C (HVC)
HIV/AIDS	human T-lymphotropic virus 1 (HTLV-1)
MALARIA	variant CJD (VCJD)
SYPHILIS	
west Nile virus	

See also BLOOD AUTODONATION; BLOOD DONATION; BONE MARROW DONATION; BONE MARROW TRANSFUSION; DISSEMINATED INTRAVASCULAR COAGULATION (DIC); HEMAPHERESIS; STEM CELL.

blood type The pattern of specialized proteins, called agglutinogens or antigens, present on the surface of the red BLOOD cells (erythrocytes). The presence of antigens on the erythrocytes causes the IMMUNE SYSTEM to create oppositional antibodies, which will attack cells bearing the opposing antigens. Antigens and corresponding antibodies begin to develop shortly following birth. The discovery of blood types in the early 1900s made successful BLOOD TRANSFUSION possible, earning researcher Karl Landsteiner (1868–1943) the 1930 Nobel Prize in medicine or physiology. Landsteiner was also among the group of scientists who discovered the rhesus (Rh) factor, another red blood cell antigen, in the 1940s.

ABO Blood Types

There are four blood types: A, B, AB, and O. Each designates the presence or absence of specific blood antigens and antibodies. Each type causes an immune reaction to blood from its opposite type. The exception is type O blood, which has no antigens on its cell surfaces. Type AB blood has antigens A and B on its cell surfaces. Doctors sometimes refer to people who have type O blood as universal donors because people of any blood type can receive emergency transfusions of type O blood (preferably as packed red blood cells containing little of the antibody-carrying PLASMA), and people who have type AB blood as universal recipients because they can receive blood of any type in emergency transfusions.

ABO BLOOD TYPES

Blood Type	Antigens on Erythrocytes	Antibodies in Plasma
A	A	anti-B
B	B	anti-A
AB	A and B	none
O	none	anti-A and anti-B

Rh Blood Types

Blood typing further incorporates tests for the presence or absence of a group of antigens known collectively as the rhesus (Rh) factor. The name derives from the rhesus monkey, the animal in which researchers first isolated the antigens. When the antigens are present on the erythrocytes the designation is Rh positive (Rh+); when the antigens are not present the designation is Rh negative (Rh–). Less than 15 percent of the American population has Rh– blood. Though collectively there are more than 40 identified antigens in the Rh blood type system, nearly all antibody response arises from Rh-D antigens. Most blood type classifications represent the ABO type and Rh status together, as in AB+ or O–.

An immune response occurs when Rh+ and Rh– blood mingle, irrespective of the ABO blood type. The health risk is to the individual whose blood is Rh–. Rh incompatibility is a serious threat to the life of an unborn child and can manifest when a mother who is Rh– conceives a child who is Rh+. The first commingling of Rh-incompatible blood typically does not result in adverse effects because the mother's Rh– blood does not yet contain antibodies against the fetus's Rh+ blood, but the first exposure to Rh+ blood activates ANTIBODY production in the mother. The first child in an Rh-incompatible pregnancy typically is born without complications; however, subsequent pregnancies result in the mother's body producing massive Rh+ antibodies that cross the PLACENTA and destroy the fetus's Rh+ erythrocytes. This condition, called hemolytic disease of the newborn (HDN) or erythroblastosis fetalis, often kills the unborn child.

The standard of PRENATAL CARE in the United States includes blood tests to determine maternal Rh status, with an injection of Rh IMMUNOGLOBULIN to prevent antibody formation in women who have Rh– blood. Rh incompatibility also can cause transfusion reaction when a person who has Rh– blood receives Rh+ blood. Such transfusion reactions can cause serious ANEMIA and cell agglutination (clumping) that can result in death.

Distribution of Blood Types

The most common blood type among Americans is O+ (38 percent); the least common is AB– (1 percent). Genes determine blood type (ABO as well as Rh). Before the advent of DNA sequencing and HUMAN LEUKOCYTE ANTIGENS (HLAS) typing, blood type was the basis of paternity testing. There are enough variations in blood type INHERITANCE PATTERNS, however, to make blood type less than 100 percent reliable for determining parentage, and blood type is no longer legal proof of parentage in the United States.

PERCENTAGES OF BLOOD TYPES AMONG AMERICANS

type O+	38 percent
type A+	34 percent
type B+	9 percent
type O–	7 percent
type A–	6 percent
type AB+	3 percent
type B–	2 percent
type AB–	1 percent

Source: American Association of Blood Banks, 2005

See also BLOOD AUTODONATION; BLOOD DONATION.

bone marrow The semigelatinous tissue within the center of the BONE. Though its presence is imperceptible in health, the bone marrow is the

foundation of the BLOOD and its circulation and plays a fundamental role in immune function. Red bone marrow is the primary source of new blood cells and is most abundant within the sternum, ribs, vertebrae, and pelvis in an adult. In childhood the bones of the skull and face, and the long bones of the arms and legs, also contain red bone marrow. As the body matures the red bone marrow in these sites transitions to yellow bone marrow, which contains mostly connective tissue and fat. The healthy adult has less than half as much red bone marrow as blood.

About 99 percent of the red bone marrow's output is erythrocytes; erythropoiesis is the process of producing erythrocytes. The red bone marrow also produces platelets (clotting cells) and granulocytes, a type of LEUKOCYTE (white blood cell). The cells that make up the bone marrow are BLOOD STEM CELLS, which continuously replicate to replenish the bone marrow and differentiate into three parent lines, or precursors, that produce blood cells. The parent lines are

- erythroblasts, which produce erythrocytes
- megakaryoblasts, which produce platelets
- myeloblasts, which produce neutrophils, basophils, and eosinophils (the three subtypes of granulocytes)

The red bone marrow also warehouses plasma cells, which are integral to immune function (not related to the PLASMA that forms the fluid base of blood). The red bone marrow is the location where B-cell lymphocytes, which migrate to the marrow from the LYMPH tissues that produce them, come to maturity. Yellow bone marrow produces a few leukocytes in adulthood though primarily functions as a reserve resource for new blood cell production when the red bone marrow cannot meet the body's needs.

DISORDERS THAT AFFECT THE BONE MARROW

ANEMIA	LEUKEMIA
LEUKOPENIA	metastatic CANCER
MULTIPLE MYELOMA	MYELODYSPLASIA SYNDROME
MYELOFIBROSIS	NEUTROPENIA
POLYCYTHEMIA VERA	radiation toxicity
THROMBOCYTHEMIA	THROMBOCYTOPENIA

For further discussion of the bone marrow within the context of blood and lymph structure and function please see the overview section "The Blood and Lymph."

See also CELL STRUCTURE AND FUNCTION; ERYTHROPOIETIN (EPO); HEMATOPOIESIS; SPLEEN.

bone marrow donation The withdrawal of BONE MARROW from a donor for use as a BONE MARROW TRANSPLANTATION or to harvest BLOOD STEM CELLS, usually as treatments for LEUKEMIA, lymphoma, some other cancers, and severe forms of ANEMIA. BONE marrow donation may be autologous (donated for reimplantation into the donor) or allogeneic (donated for another person to receive as a bone marrow transplantation).

Bone marrow donation is a surgical procedure performed in an operating room under general ANESTHESIA. The physician extracts donor bone marrow, which is a thick liquid, using a syringe and a large needle that can pierce the bone. The most common donor site is the iliac crest (hip bone). A single bone marrow donation typically harvests about 1 quart (less than a liter) of red bone marrow mixed with BLOOD. The donor's body replaces the extracted marrow in about four to six weeks. The risks of bone marrow donation are slight. They include postoperative bleeding and INFECTION. The withdrawal site is typically uncomfortable for a few days after the donation.

There is no cost to the donor for the bone marrow donation procedure and care related to it unless the donor is also to be the recipient (autologous donation). Prospective donors register with a bone marrow donor program, which uses blood samples to identify tissue types. The program contacts the prospective donor when there is a need for marrow of his or her tissue type. Unlike blood donated for transfusions, bone marrow cannot be stored.

A less invasive type of donation that appears to achieve the same result is peripheral blood stem cell (PBSC) collection, done through a procedure called HEMAPHERESIS (also called apheresis). Hemapheresis is similar to BLOOD DONATION, in which an intravenous (IV) line withdraws the donor's blood. The blood goes into a blood separator that extracts the blood stem cells and returns the remainder of the blood to the donor via a second

IV line in a different VEIN. Before PBSC the person may receive injections of a medication to stimulate the bone marrow to increase its production of blood stem cells, to increase their numbers in the blood. The blood yields a lower volume of blood stem cells than does bone marrow.

See also BLOOD TRANSFUSION.

bone marrow transplantation A therapeutic procedure to replace the BLOOD STEM CELLS, the functional component of BONE MARROW, with healthy donor BLOOD stem cells. Typically the preparation process for the BONE marrow removes T-cells and sometimes other leukocytes (white blood cells) to lower the likelihood of ANTIGEN response in the recipient. Common reasons for bone marrow transplantation include

- some types of LEUKEMIA
- some types of lymphoma
- some other cancers that have not responded to first line treatments
- severe aplastic ANEMIA

Bone marrow transplantation is a complex and fairly high-risk procedure because the recipient's native bone marrow must first be destroyed, which wipes out the body's IMMUNE RESPONSE capability. Doctors accomplish this through high-DOSE CHEMOTHERAPY or RADIATION THERAPY. After this preparation, the recipient must remain in protective isolation in the hospital to limit exposure to pathogens such as viruses and BACTERIA.

The transplant recipient receives the bone marrow blood stem cells, tissue-matched for compatibility between donor and recipient, via infusion into an intravenous line, much like receiving a BLOOD TRANSFUSION. The transplanted blood stem cells migrate to the bone marrow where they establish themselves (a process called engraftment). The migration and engraftment takes about three to four weeks, after which the transplanted blood stem cells begin producing new blood cells. The immune functions of the bone marrow and blood cells begins to return in about six months, though is not complete for as long as two years. During this replenishment stage the person remains especially vulnerable to INFECTION. As well, some people take IMMUNOSUPPRESSIVE THERAPY to reduce the risk for rejecting the transplanted blood stem cells. Immunosuppression further limits the immune response.

The primary risks of allogeneic (volunteer donor) bone marrow transplantation are infection and, with allogeneic donation, rejection of the transplanted blood stem cells. There is no risk for rejection with autologous donation. Infection, however, can erupt at any time and has high risk for serious or fatal consequences for as long as the person's immune response cannot provide protection. Early intervention with ANTIBIOTIC MEDICATIONS can head off or reduce the severity of many bacterial infections. Frequent blood tests monitor the return of healthy blood cells to the circulation. The success of bone marrow transplantation is highly variable and depends on numerous factors, including the kind of cancer and the general health of the person aside from the cancer. When successful, bone marrow transplantation can put the cancer into extended and sometimes permanent REMISSION.

See also BONE MARROW DONATION; CANCER TREATMENT OPTIONS AND DECISIONS; GRAFT VS. HOST DISEASE; ORGAN TRANSPLANTATION.

C

Christmas disease See HEMOPHILIA.

cisterna chyli A saclike structure of the lymphatic system, located behind the STOMACH, that collects LYMPH draining from the abdomen, notably the gastrointestinal region, and the lower body. The cisterna chyli empties into the THORACIC DUCT.

For further discussion of the cisterna chyli within the context of blood and lymph structure and function please see the overview section "The Blood and Lymph."

See also LYMPHEDEMA; LYMPH VESSELS; RIGHT LYMPHATIC DUCT.

clotting factors Proteins in the BLOOD that are essential for COAGULATION. Clotting factors circulate in the blood as inert proteins until the coagulation cascade initiates their conversion into participants

CLOTTING FACTORS

Clotting Factor	Common Name	Function
antithrombin	antithrombin III, antithrombin III, COAGULATION inhibitor, AT-III	regulates thrombin, factor IX, factor X, factor XI, and factor XII to inhibit the coagulation cascade
factor I	fibrinogen	forms fibrin clot after activation by thrombin in the final common pathway
factor II	prothrombin	together with factor Xa prothrombinase converts prothrombin into active thrombin, which in turn helps PLATELET AGGREGATION
factor III	tissue factor	initiates extrinsic coagulation cascade following vascular injury cofactor with factors VII, VIII, and IX in activating factor X cofactor in activation of factor VII
factor IV	calcium	required at several points in the coagulation cascade
factor V	proaccelerin or accelerator globulin	necessary to stop coagulation cascade at the end
factor VI	accelerin, factor Va	activated form of factor V together with factor X converts prothrombin to thrombin in the final common pathway

Clotting Factor	Common Name	Function
factor VII	serum prothrombin conversion accelerator (SPCA) or cothromboplastin	activates factor X when calcium and factor III (tissue factor) are present
factor VIII	antihemophilic factor A	activates platelet aggregation and adhesion cofactor with factor IX in activating factor X
factor IX	Christmas factor, antihemophilic factor B, or plasma thromboplastin component (PTC)	cofactor with factor VIII in activating factor X (vitamin K-dependent)
factor X	Stuart factor or Stuart-Prower factor	activated by complex of tenase (factors VII and IX), factor VII, and calcium to enable platelet aggregation Initiates conversion of factor II (prothrombin) to thrombin
factor XI	plasma thromboplastin antecedent (PTA)	in the intrinsic pathway, activates factor IX when calcium is present
factor XII	Hageman factor	activates factor XI, thereby starting the intrinsic pathway binds to exposed collagen at site of intravascular injury
factor XIII	fibrin stabilizing factor (FSF), fibrinoligase, fibrinase, plasma transglutaminase, Laki-Lorand factor, LL factor, LLF, or protransglutaminase	cross-links and stabilizes fibrin clot after activation by thrombin needs calcium as cofactor
high molecular weight kininogen (HMWK)	contact activation factor, Fitzgerald factor, Flaujeac factor, Williams-Fitzgerald-Flaujeac factor, or Williams factor	activates factor XII early in the intrinsic pathway
prekallikrein	Fletcher factor or prokallikrein	activates factor XII at very beginning of the intrinsic pathway
protein C	anticoagulant protein C	limits functions of factor V and factor VIII with cofactor protein S, inhibits thrombin to block fibrin clot formation
protein S	anticoagulant cofactor protein S	limits functions of factor V and factor VIII as cofactor for protein C, inhibits thrombin to block fibrin clot formation
thrombomodulin	fetomodulin	cell surface receptor that binds excess thrombin, thus inhibiting dangerous clot formation

in blood clotting. Clotting factors interact with each other as well as other enzymes in the blood, notably fibrin and thrombin, to form blood clots. Deficiencies of specific clotting factors cause coagulation disorders such as HEMOPHILIA (excessive bleeding) and thrombophilia (excessive clot formation). The LIVER produces clotting factors I (fibrinogen), II (prothrombin), V (proaccelerin), VII (cothromboplastin), IX (PLASMA thromboplastin), and X (Stuart-Prower factor).

See also ANTICOAGULANT THERAPY; ASPIRIN THERAPY.

coagulation The process, also called the coagulation cascade, through which the BLOOD forms clots. The cells responsible for forming clots are platelets, which interact with each other, collagen, proteins, and other substances in the blood. Specialized proteins in the blood, called CLOTTING FACTORS, activate in cascades, with one activation leading to another in sequence. Coagulation begins with one of two sequences of cascading events: either an extrinsic or an intrinsic trigger sets off a different cascade. Each cascade culminates in clot formation. Current research suggests that coagulation cascades unfold at different paces and with differing thresholds of activation according to the type of tissue or the organ structure involved. This way, the body manages the coagulation process appropriately to the situation.

Coagulation is a beneficial event when it stops bleeding and can become a hazard to health when it occurs inside blood vessels. Insufficient clotting allows extended bleeding, and excessive clotting can result in HEART ATTACK, STROKE, PULMONARY EMBOLISM, and DEEP VEIN THROMBOSIS (DVT). Though the coagulation process includes several inherent checks and balances that ordinarily strike a balance between beneficial and harmful clotting, problems with coagulation can occur and can be life-threatening.

Coagulation disorders occur when certain clotting factors are missing (such as in HEMOPHILIA), which results in excessive bleeding, or when there is an abundance of platelets in the blood (such as in THROMBOCYTHEMIA), resulting in excessive clotting. LIVER disease such as CIRRHOSIS or severe HEPATITIS affects the liver's ability to produce clotting factors—especially factors II, VII, and X—and to metabolize VITAMIN K (which participates in converting a number of clotting factors from inactive to active states), impairing coagulation.

Extrinsic coagulation cascade Any breach in a blood vessel, such as a cut (even microscopic), causes blood to come into contact with tissue factor (clotting factor III), a protein on the surface of epithelial cells (the cells of the SKIN, mucous membranes, and lining of the blood vessels). Tissue factor initiates the extrinsic coagulation cascade, activating the release and interactions of thromboplastin, clotting factor VII, and calcium ions to culminate in the production of clotting factor X.

Intrinsic coagulation cascade Internal clot formation occurs without a breach when the blood comes into contact with a foreign substance in the blood such as an ATHEROSCLEROTIC PLAQUE that activates the body's INFLAMMATION response, resulting in the formation of collagen. Collagen's presence initiates the release of kallikrein and high molecular weight kininogen (HMWK), two substances that activate clotting factor XII. The continued interaction among these substances draws clotting factor XI and clotting factor IX into the process, culminating in the production of clotting factor X.

Clot formation PLATELET AGGREGATION and clot formation begin at the intermediate level of either cascade, when clotting factor X initiates the conversion of clotting factor II (prothrombin) into the enzyme thrombin. Thrombin in turn converts clotting factor I (fibrinogen) to fibrin, a protein that interlaces with collagen (formed by the IMMUNE SYSTEM's inflammation response) to form a clot. The clot attracts additional platelets, extending the coagulation process until the protein thrombomodulin activates protein C, beginning the coagulation inhibition cascade that brings coagulation to a halt.

See also ANTICOAGULATION THERAPY; ASPIRIN THERAPY; CORONARY ARTERY DISEASE (CAD); C-REACTIVE PROTEIN; HEALING; MEDICATIONS TO TREAT CARDIOVASCULAR DISEASE; SCAR.

D–G

disseminated intravascular coagulation (DIC) A secondary COAGULATION disorder arising from an imbalance among the CLOTTING FACTORS in the BLOOD. DIC occurs as a result of a significant underlying health condition such as HIV/AIDS, overwhelming infections, or CANCER, and as a serious complication in PREGNANCY. DIC is a symptom rather than a condition. Indications of its presence include

- PETECHIAE (pinpoint hemorrhages), especially on the roof of the MOUTH (soft palate) and the lower legs
- ECCHYMOSIS (easy bruising)
- hemorrhage (easy bleeding)
- thrombosis (clot formations in the blood vessels, typically the veins)

The diagnostic path includes blood tests, especially fibrinogen and fibrin split products. Treatment for DIC targets the underlying cause, though may include measures such as BLOOD TRANSFUSION to arrest hemorrhaging or ANTICOAGULATION THERAPY when the condition manifests as thrombosis. The outlook, like the treatment, depends on the underlying cause.

See also PLATELET.

eosinophil See GRANULOCYTE.

erythrocyte A red BLOOD cell (RBC). The primary function of erythrocytes is to carry oxygen from the LUNGS to the cells of tissues throughout the body and return carbon dioxide, a metabolic waste, to the lungs for removal from the body. Erythrocytes contain iron and HEMOGLOBIN, a pigmented protein that gives them their red color. Hemoglobin is the substance to which oxygen and carbon dioxide molecules bind for transport through the bloodstream. Erythrocytes account for 99 percent of the blood cells the blood carries.

Erythrocytes lack nuclei, which means they cannot proliferate (reproduce). They have a lifespan of about 120 days. The BONE MARROW thus must continuously produce erythrocytes, which it does at the rate of about 2 million per minute. The SPLEEN and the LIVER filter aging, deteriorating, and defective erythrocytes from the blood circulation. Men have a somewhat higher percentage of erythrocytes in their blood, about 47 percent, than women, who have about 42 percent, primarily because women lose blood each month with MENSTRUATION. The number of erythrocytes in both men and women begins to decline after age 70 because erythropoiesis slows as a natural aspect of aging.

For further discussion of erythrocytes within the context of blood and lymph structure and function please see the overview section "The Blood and Lymph."

See also HEMATOPOIESIS; OXYGEN–CARBON DIOXIDE EXCHANGE.

erythropoiesis See HEMATOPOIESIS.

erythropoietin (EPO) A HORMONE the KIDNEYS produce that stimulates the BONE MARROW to increase red BLOOD cell production. EPO is a protein structure called a CYTOKINE. Specialized cells in the renal cortex, called peritubular fibroblasts, respond to the amount of oxygen in the blood as it passes through the kidney. When the oxygen saturation of the blood is low (HYPOXIA), the peritubular fibroblasts increase EPO production. Normally the bone marrow releases about two million

erythrocytes into circulation every minute. The EPO stimulates the bone marrow to release higher numbers of erythrocytes into the blood circulation, which boosts the amount of HEMOGLOBIN and increases the blood's capacity to carry oxygen.

EPO production falters in serious kidney disease, resulting in ANEMIA. Medications that diminish kidney function may have similar effects. The liver and perhaps other sites in the body also produce small amounts of EPO, though not enough to meet the body's needs when the kidneys fail. Some people experience fluctuations in EPO production, both increases and decreases, after KIDNEY TRANSPLANTATION.

During the 1980s researchers identified and sequenced the GENE responsible for EPO, allowing the synthesis of recombinant erythropoietin in the laboratory. Administered by injection, this form of EPO, epoetin alpha (Procrit, Epogen), can supplement or replace endogenous EPO to stimulate the bone marrow when kidney production falls off or other circumstances cause rapid ERYTHROCYTE depletion and corresponding anemia. Potential side effects of EPO supplementation include increased BLOOD PRESSURE (HYPERTENSION) especially when the cause of anemia is RENAL FAILURE, and thrombosis (the formation of blood clots within the blood vessels) resulting from the increased percentage of erythrocytes in the blood.

See also BLOOD DOPING; CYTOKINES; HEMATOPOIESIS; MULTIPLE MYELOMA.

granulocyte A type of LEUKOCYTE (white BLOOD cell) so named because its cytoplasm contains granules. The granules, called lysosomes in neutrophils, contain enzymes that digest proteins and carbohydrates, the basic components of cellular structures. Granulocytes are primarily phagocytic; their responsibility is to consume pathogens that lymphocytes and other leukocytes neutralize as part of the body's IMMUNE RESPONSE. Pathologists refer to granulocytes as polymorphonuclear (PMN) because the nucleus of a granulocyte contains multiple lobes. Granulocytes have a short life span in the circulation, typically six to eight hours. After this time some of them migrate into the tissues and continue to function as phagocytes. The liver filters from circulation those that do not migrate and its phagocytic cells, the Kupffer cells, consume them. There are three types of granulocytes, named for the kinds of tissue dyes they accept to emphasize their structures for microscopic examination: basophils, eosinophils, and neutrophils.

Basophils A basophil accepts a base dye such as methylene blue, accounting for its name, which means "base-loving." Basophils respond to the various chemicals injured cells and pathogens release, among them HISTAMINE, serotonin, CYTOKINES, LEUKOTRIENES, and PROSTAGLANDINS. Basophils themselves also release these chemicals, which serves to further incite an inflammatory response as well as summon more leukocytes into action. Basophils filled with HISTAMINE granules are primarily responsible for HYPERSENSITIVITY REACTION and ALLERGY responses. They are abundant in the bronchial tissues during ASTHMA attacks, for example, and in the tissues surrounding an insect bite or sting.

Eosinophils The eosinophil ("eosin-loving") accepts a tissue dye called eosin for examination under the light microscope. Eosinophils, containing enzymes to digest bacteria and other pathogens, also have roles in histamine release (such as in hypersensitivity reactions and asthma) and inflammatory response. Parasitic infections, atopic DERMATITIS, non-Hodgkin's LYMPHOMA, and OVARIAN CANCER are among the conditions that can cause elevated eosinophil levels. Medication reactions, notably with beta blockers and CORTICOSTEROID MEDICATIONS, are among the causes of lowered eosinophil levels. An eosinophil normally circulates about eight hours in the blood and then migrates into the tissues.

Neutrophils The neutrophil ("neutral-loving") stains neutrally for microscopic examination. It is the most abundant type of leukocyte in the blood, making up about 70 percent of the white blood cells in circulation. Neutrophils are the IMMUNE SYSTEM's infantry, maintaining a strong defensive presence in the blood and swarming to attack invading pathogens. Neutrophils that die in the line of duty release toxic chemicals to continue their protective actions. Neutrophils are integral to the body's inflammatory response and are often to blame for autoimmune attacks such as those that occur with RHEUMATOID ARTHRITIS and INFLAMMATORY BOWEL DISEASE (IBD). Numerous health conditions can lower the number of neutrophils in the blood circulation

including infections, serious vitamin B deficiency, RADIATION THERAPY, CHEMOTHERAPY, and cancers such as LEUKEMIA and lymphoma. Some medications, notably antibiotics and NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS), can also decrease the neutrophil level raising the risk for INFECTION.

For further discussion of granulocytes within the context of blood and lymph structure and function please see the overview section "The Blood and Lymph."

See also CELL STRUCTURE AND FUNCTION; LYMPHOCYTE; MONOCYTE.

H

hematopoiesis The process through which the body generates new BLOOD cells. In the adult, the red BONE MARROW and the LYMPH tissues (primarily the lymph nodes and the SPLEEN) manufacture the blood cells the body needs, with extramedullary resources for ERYTHROCYTE production available as reserves from the LIVER, spleen (erythrocytes), and yellow BONE marrow. Researchers do not fully understand the mechanisms of hematopoiesis though know complex interactions of hormones, proteins, and chemicals regulate the processes by which the body makes new blood cells. There are two major divisions of hematopoiesis: erythropoiesis (production of erythrocytes) and leukopoiesis (production of leukocytes).

Pluripotency, Differentiation, and Proliferation

As best researchers understand the mechanisms of hematopoiesis, all blood cells arise from pluripotent BLOOD STEM CELLS that have the ability to develop into any of the blood cell types. The first level of hematopoiesis occurs when a blood stem cell either proliferates, extending the volume of pluripotent cells, or differentiates into one of two committed lineages, myeloid or lymphoid. The lymphoid lineage will produce lymphocytes and monocytes, and the myeloid lineage will produce erythrocytes, granulocytes (basophils, eosinophils, and neutrophils), and platelets. Each lineage generates a number of differentiations or stages of development. The length of time it takes for a pluripotent cell to produce a mature blood cell varies with the type of blood cell and other physiologic factors, ranging from 6 days for an erythrocyte to 14 days for a neutrophil.

Erythropoiesis

Erythropoiesis begins with committed myeloid cells that differentiate into myeloblasts or proerythrocytes. Myeloblasts will become granulocytes,

HEMATOPOIETIC STRUCTURES

Hematopoietic Structure	Blood Cells the Structure Produces
red BONE MARROW	erythrocytes, platelets, granulocytes, some monocytes
LIVER	erythrocytes on demand (extramedullary resource)
LYMPH nodes	lymphocytes, monocytes
SPLEEN	lymphocytes, monocytes erythrocytes on demand (extramedullary resource)
THYMUS	lymphocytes
yellow bone marrow	limited leukocytes erythrocytes and platelets on demand (extramedullary resource)

the majority of which will be neutrophils. Proerythrocytes will become erythrocytes (more than 99 percent) or platelets (less than 1 percent). Numerous substances influence and regulate erythropoiesis. Among them are

- ERYTHROPOIETIN (EPO), a HORMONE the KIDNEYS secrete that stimulates the bone marrow to increase differentiation of proerythrocytes and thus increase erythrocyte production
- intrinsic factor, or erythrocyte-maturing factor, which the STOMACH secretes to facilitate erythrocyte maturation
- vitamin B_{12}, also called extrinsic factor, which interacts with intrinsic factor
- iron, which is an essential component of HEMOGLOBIN (the protein complex within erythrocytes that binds with oxygen)

An erythrocyte goes through several stages of development before reaching a mature enough stage, that of reticulocyte, to leave the bone marrow. After 24 hours in circulation in the blood, the reticulocyte evolves to its final stage of maturity and becomes a fully functional erythrocyte. Erythrocytes circulate in the blood for about 120 days. The red bone marrow releases 2 million reticulocytes per minute into the blood circulation; the spleen extracts a comparable number of old erythrocytes from the circulation to maintain the correct proportion of erythrocytes in the blood.

Platelets arise from proerythrocytes that differentiate to become megakaryoblasts and then megakaryocytes. The megakaryocytes release fragments of their cytoplasm, which become platelets. While megakaryocytes are the largest cells in the bone marrow, platelets are the smallest particles in the blood. The spleen retains about 30 percent of the platelets the bone marrow produces, releasing them when a COAGULATION cascade sends chemical signals summoning platelets to the site of clot formation.

Leukopoiesis

Leukopoiesis, the production of white blood cells, takes place in both the bone marrow (granulocytes) and the lymph tissues (monocytes and lymphocytes). In general, all three types of leukocytes make up less than 1 percent of the blood cells in circulation. Many factors influence leukopoiesis, including immune status and whether an INFECTION is present in the body. Leukocytes also undergo a series of developmental evolutions before reaching maturity. Lymphocytes the lymph tissues release are immature and migrate to the THYMUS (T-cell lymphocytes) or the bone marrow (B-cell lymphocytes) to mature.

DISORDERS OF HEMATOPOIESIS

AMYLOIDOSIS	ANEMIA
BONE MARROW failure	LEUKEMIA
LEUKOPENIA	LYMPHOCYTOPENIA
LYMPHOMA	MULTIPLE MYELOMA
MYELODYSPLASIA SYNDROME	MYELOFIBROSIS
NEUTROPENIA	POLYCYTHEMIA VERA
THROMBOCYTHEMIA	THROMBOCYTOPENIA
vitamin B_{12} deficiency	

See also CELL STRUCTURE AND FUNCTION; HEMOLYSIS.

hemapheresis The process of withdrawing BLOOD from the body, filtering it through a machine called a cell separator to extract a desired blood component, and returning the rest of the blood to the person. There are two forms of hemapheresis, therapeutic and donor. Therapeutic hemapheresis, also called apheresis, removes damaged or defective components from the blood, which allows the body to naturally replace the components with healthy structures. Donor hemapheresis collects blood components for use in BLOOD TRANSFUSIONS.

CLINICAL APPLICATIONS FOR THERAPEUTIC HEMAPHERESIS

GLOMERULONEPHRITIS	GOODPASTURE'S SYNDROME
hyperviscosity	LEUKEMIA
MALARIA	MULTIPLE SCLEROSIS
MYASTHENIA GRAVIS	organ transplant rejection
PEMPHIGUS vulgaris	protein-bound DRUG toxicity
RHEUMATOID ARTHRITIS	SICKLE CELL DISEASE
thrombocytosis	thrombotic thrombocytopenic
transfusion reaction	PURPURA

For hemapheresis, the phlebotomist inserts an intravenous needle into a VEIN in each arm. One needle attaches to tubing that allows blood to flow out of the body and into the cell separator. The other needle attaches to tubing that brings the

blood back to the body after the cell separator has extracted the appropriate blood product. The entire process takes about two hours for most blood products. Some people find insertion of the needles uncomfortable and may also have chills and mild discomforts during the hemapheresis or for a short time afterward. There are relatively few risks with hemapheresis.

KINDS OF HEMAPHERESIS

cytapheresis	=	removal of cells
leukapheresis	=	removal of leukocytes (white blood cells)
plasmapheresis	=	removal of plasma
plateletapheresis	=	removal of platelets

See also BLOOD DONATION; HEMOCHROMATOSIS; PHLEBOTOMY.

hematoma Bleeding into the tissues that forms a contained mass. Most superficial hematomas are benign, such as the common hematoma auris, involving the auricle (outer EAR) and BLACK EYE, involving the orbital tissues surrounding the EYE. Such hematomas typically occur as the consequence of blows to the tissues that cause BLOOD vessels to break. As the blood coagulates the mass hardens. A hematoma may take weeks to several months to fully resolve as the body works to dismantle the clot. Most superficial hematomas do not require medical care, though a doctor should evaluate any injury that potentially involves the eye or symptoms of HEARING LOSS.

An internal hematoma that occurs within the skull (subdural or subarachnoid hematoma) is particularly dangerous and even life-threatening because it causes increased pressure that damages the BRAIN. Hematomas that occur within major organs such as the LIVER or the SPLEEN are also serious. These hematomas may be the result of trauma or may occur because of anomalous blood vessel structures (such as hemangioma) that spontaneously rupture. Internal hematomas require medical evaluation and careful monitoring. The doctor may recommend surgical removal of hematomas that threaten the function of vital organs such as the brain or the liver.

See also BRAIN HEMORRHAGE; ECCHYMOSIS; PETECHIAE; PURPURA; STROKE; TRAUMATIC BRAIN INJURY (TBI).

hemoglobin A combined protein within erythrocytes (red BLOOD cells) that is crucial to the OXYGEN–CARBON DIOXIDE EXCHANGE. Two proteins come together to form hemoglobin: heme, a reddish pigment that contains iron, and globin. Hemoglobin bonds loosely with oxygen and carbon dioxide molecules, depending on which is in higher concentration.

In the LUNGS, oxygen molecules have the higher concentration and bind with the hemoglobin. As the blood carries the erythrocytes deeper into the body where oxygen concentrations are lower, the bond becomes less stable. When the erythrocytes reach the CAPILLARY BEDS where the concentration of carbon dioxide is higher than the concentration of oxygen, the hemoglobin releases its oxygen molecules and replaces them with carbon dioxide molecules and carries the carbon dioxide back to the lungs where the exchange repeats.

Cigarette smoke contains high levels of carbon monoxide. Heavy smokers may have blood concentrations of carbon monoxide of 7 to 9 percent.

Carbon monoxide binds more strongly with hemoglobin than oxygen or carbon dioxide, forming a tight bond (the compound carboxyhemoglobin) that blocks hemoglobin from binding with either. Only small amounts of carbon monoxide inhaled into the lungs can interfere with the oxygen–carbon dioxide exchange significantly enough to cause poisoning (HYPOXIA) or death. Carbon monoxide begins to cause symptoms of oxygen deprivation when its blood concentration reaches 10 percent, impairs neurologic function at 30 percent, and can cause death at 50 percent. A gas commonly present in the environment, carbon monoxide is a byproduct of incomplete combustion.

See also ANEMIA; HEMOCHROMATOSIS; INHALED TOXINS; SICKLE CELL DISEASE; SMOKING AND HEALTH; THALASSEMIA.

hemolysis The destruction and disassembly of erythrocytes (red BLOOD cells). Erythrocytes live in the blood for about 120 days after their release from the BONE MARROW. At the end of this time they either die or the SPLEEN culls them from circu-

lation. The spleen partially dismantles the erythrocytes, reducing toxic heme into BILIRUBIN that the body excretes with the BILE. The LIVER then recycles these components for numerous other uses in the body. Accelerated hemolysis, which results in ANEMIA, can occur with, or characterizes, various disorders.

CONDITIONS IN WHICH HEMOLYSIS MAY OCCUR

adverse DRUG reactions	BLOOD enzyme disorders
BLOOD TRANSFUSION reaction	ERYTHROCYTE metabolic disorders
HEMOGLOBIN disorders	IMMUNE SYSTEM dysfunction
SEPTICEMIA	SICKLE CELL DISEASE
SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)	THALASSEMIA

See also APOPTOSIS; CELL STRUCTURE AND FUNCTION; PHAGOCYTOSIS; SPLENOMEGALY.

hemophilia A group of inherited GENETIC DISORDERS in which certain CLOTTING FACTORS are deficient or absent, resulting in clotting dysfunction. People who have hemophilia tend to bleed easily and longer than normal. Some forms of hemophilia carry substantial risk for life-threatening hemorrhage (bleeding).

Types of hemophilia Doctors classify hemophilia according to the deficient clotting factor, which may be missing from the BLOOD, present in subnormal quantities, or present but defective. About 85 percent of people who have hemophilia have hemophilia A, a deficiency of clotting factor VIII (also called antihemophilic factor A). The remaining 15 percent have hemophilia B, a deficiency of clotting factor IX (also called Christmas factor, antihemophilic factor B, or PLASMA thromboplastin). Hemophilia B was once called Christmas disease—named after the family in which doctors first identified the clotting factor IX deficiency—and distinguished this type of hemophilia from the classic hemophilia A. Hemophilia C, which is very rare in the United States, is a deficiency of clotting factor XI (also called plasma thromboplastin antecedent).

Inheritance patterns The most common types of hemophilia, hemophilia A and hemophilia B, are inherited X-linked CHROMOSOMAL DISORDERS, meaning they nearly always only affect males. The daughters of a man who has hemophilia A or B will all carry the defective GENE, though the sons will have normal clotting factor genes. The son of a carrier has a 50 percent chance of having hemophilia; the daughter of a carrier has a 50 percent chance of also carrying the defective genes. Rarely, hemophilia A or B occurs through spontaneous gene MUTATION. In such circumstances it is possible for a woman to have the disorder. Hemophilia C, which primarily affects people who are of Ashkenazi Jewish descent, is an autosomal disorder that affects men and women equally though is very rare.

Symptoms and Diagnostic Path

Excessive bleeding is the most common symptom of hemophilia A or B, which often first manifests after CIRCUMCISION. The more severe the hemophilia, the earlier in life symptoms become apparent. Some men may not experience symptoms until adulthood, while others experience life-threatening hemorrhage with common childhood injuries such as nosebleed (EPISTAXIS) and trauma such as a cut. The diagnostic path includes blood tests that measure clotting times, PLATELET AGGREGATION, blood cell counts, and the presence of clotting factors VIII, IX, and XI, and the von Willebrand factor. The findings of these tests, along with personal and family medical histories, are generally conclusive of the diagnosis.

The amount of functional clotting factor in the blood determines the severity of the hemophilia. Clotting factor presence above 10 percent generally produces only mild to moderate symptoms; clotting factor presence below 1 percent, which occurs in about 70 percent of people who have hemophilia, generally produces severe symptoms. Life-threatening hemorrhage is the most significant consequence of hemophilia.

Treatment Options and Outlook

The goal of treatment is generally to raise the deficient clotting factor to 30 percent, or 50 to 100 percent during episodes of active bleeding, depending on the site. Treatment may be transfusions with fresh frozen plasma or plasma cryoprecipitate, both of which contain clotting factors VIII and IX, or with clotting factor concentrates. The more often these treatments are necessary, however, the greater the likelihood the person will

develop antibodies to the clotting factors that subsequently prevents these treatments from having any effect. In such situations the doctor may administer porcine-derived forms of clotting factor VIII or prothrombin complex concentrate, which bypass some of the steps in the coagulation cascade to avoid ANTIBODY activation.

A promising treatment for mild hemophilia A is the synthetic HORMONE desmopressin. Also called DDAVP, desmopressin is an analog (close chemical relative) of the endogenous hormone vasopressin, which the PITUITARY GLAND secretes. Administered intravenously or via nasal spray, desmopressin causes the body to increase blood levels of clotting factors VIII and IX. However, desmopressin has little effect in people who have hemophilia B. Desmopressin may affect other aspects of the coagulation cascade and can elevate the BLOOD PRESSURE.

Blood product treatments for hemophilia carry the risk of INFECTION with various pathogens that current blood screening technology cannot detect including HEPATITIS A, human T-lymphotropic virus 1 (HTLV-1), west Nile virus, MALARIA, and also CYTOMEGALOVIRUS (CMV). Though infection with human immunodeficiency virus (HIV) was a significant problem during the 1980s, screening procedures in effect today have nearly eliminated the risk for acquiring HIV/AIDS through donated blood products.

Many people who have hemophilia are able to enjoy a high QUALITY OF LIFE with ongoing medical monitoring and lifestyle choices to reduce the risk for traumatic injury. However, complications such as JOINT damage due to frequent bleeding can limit physical activities. GASTROINTESTINAL BLEEDING is also a potential complication.

Risk Factors and Preventive Measures

Genetic inheritance is the only known risk factor for hemophilia. Health experts encourage people who have hemophilia, know they carry the gene defect for hemophilia, or have a family history of unusual bleeding to discuss FAMILY PLANNING with a genetic counselor who can advise of the risks that children will either carry or have hemophilia. Much research currently focuses on perfecting recombinant technologies to provide clotting factor therapies free from risk of infection and antibody development. Other research efforts are exploring the potential for GENE THERAPY that can repair the damaged genes, though this potential has not yet yielded practical results.

See also ANTIBODY; COAGULATION; GENETIC COUNSELING; GENETIC DISORDERS; INHERITANCE PATTERNS; VON WILLEBRAND'S DISEASE.

leukapheresis See HEMAPHERESIS.

leukemia A type of CANCER that affects the BONE marrow's production of leukocytes (white BLOOD cells). Doctors classify leukemia as either myeloid (sometimes called myelocytic) or lymphocytic (sometimes called lymphoblastic), depending on the type of leukocytes affected. Within either classification leukemia can be acute or chronic. The four most common types of leukemia are

- acute lymphocytic leukemia (ALL)
- chronic lymphocytic leukemia (CLL)
- acute myeloid leukemia (AML)
- chronic myeloid leukemia (CML)

LEUKEMIA VS. LYMPHOMA

LYMPHOMA is another type of cancer that can affect the lymphocytes. However, lymphoma is a cancer of the lymphatic tissues that produce and store lymphocytes. Leukemia is a cancer of the BONE MARROW that alters the development and proliferation of the lymphocytes that enter the BLOOD circulation.

There are a number of subtypes within these classifications, usually identified according to the affected cell type or its developmental stage. Though common perception is that leukemia primarily affects children, 10 times as many adults as children develop this type of cancer. Children are more likely to develop acute leukemia and adults over age 60 to develop chronic leukemia, though either form can occur at any age. Some forms of childhood leukemia are fully curable and some forms of adult leukemia are highly manageable. GENETIC PREDISPOSITION and certain environmental factors, such as exposure to industrial chemicals, pesticides, and RADIATION THERAPY or CHEMOTHERAPY, appear to increase an individual's risk for developing leukemia. However, most of the time doctors do not know what causes this leukemia to develop.

How Leukemia Develops

All blood cells arise from pluripotent BLOOD STEM CELLS, "parent" cells within the BONE MARROW that have the ability to form into several different kinds of blood cells. A complex interaction of genetic encoding, chemicals, proteins, molecular functions, and physiologic needs determines the manner in which blood stem cells differentiate (become specific kinds of cells) and proliferate (reproduce themselves). At the first level of differentiation, a blood stem cell establishes its lineage as lymphoid or myeloid. Myeloid stem cells give rise to erythrocytes, platelets, granulocytes, and monocytes. Lymphoid stem cells give rise to lymphocytes. In leukemia, the stem cells are normal though something goes awry at the first stage of differentiation, and one of the lines—lymphoid or myeloid—produces abnormal cells.

In acute forms of leukemia the bone marrow accelerates LEUKOCYTE production and releases immature leukocytes not yet capable of functioning as leukocytes. In relatively short time the immature cells flood the bone marrow, crowding out other cells. The onset of symptoms with acute leukemia is generally rapid because the immature cells the bone marrow releases cannot function yet are entering the circulation at a rate that causes them to quickly become dominant in the blood. In chronic leukemia the bone marrow's rate of production is normal and the leukocytes the marrow releases into the circulation are mature but defective. The onset of symptoms in

chronic leukemia is usually gradual because these cells, though defective, can function to some extent and enter the blood circulation at the normal rate. In all types of leukemia, the defective cells also block the bone marrow from producing platelets and erythrocytes, resulting in dysfunctional COAGULATION (clotting) and ANEMIA.

Acute lymphatic leukemia (ALL) The most common leukemia of childhood, ALL arises when a genetically damaged lymphoid clone cell in the bone marrow proliferates, causing immature lymphocytes, called lymphoblasts or leukemic blasts, to replace healthy lymphocytes in the bone marrow and the blood circulation. The accumulation prevents normal HEMATOPOIESIS, resulting in anemia, coagulation dysfunction, and vulnerability to INFECTION. About 85 percent of ALL involves B-cell lymphocytes and the remaining 15 percent involves T-cell lymphocytes. Doctors diagnose about 4,000 people a year with ALL in the United States.

Chronic lymphatic leukemia (CLL) Doctors diagnose about 8,000 people a year with CLL in the United States, more than 75 percent of them being over the age of 60. In CLL, the proliferating defective lymphocytes function normally. CLL may generate no symptoms or ill effects, in which case doctors generally opt for watchful waiting as the treatment approach. As CLL progresses, however, it causes dysfunctional IMMUNE RESPONSE. Defective lymphocytes that accumulate in the bone marrow eventually suppress bone marrow function.

Acute myeloid leukemia (AML) The most common leukemia among people over age 40, AML arises through the proliferation of a defective myeloid clone cell and manifests in one of seven forms. Doctors designate these forms as subtypes M1 through M7, according to the cells involved. The subtype determines the course of treatment and likelihood for REMISSION. As with ALL, the proliferation of the defective clone prevents normal hematopoiesis with consequent THROMBOCYTOPENIA, anemia, and often NEUTROPENIA. Doctors diagnose about 12,000 people a year with AML in the United States.

Chronic myeloid leukemia (CML) Nearly always a cancer occurring in adulthood, CML results from the translocation of chromosomes 9 and 22, an acquired MUTATION commonly referred to as the Philadelphia, or Ph, CHROMOSOME. Researchers do not know what causes the abnormality, which produces the rampant proliferation of monocytes or granulocytes that function normally. Other hematopoiesis is normal as well. Doctors diagnose about 54,000 people a year with CML in the United States.

Symptoms and Diagnostic Path

Symptoms of leukemia develop when the cancerous cells in the blood circulation begin to outnumber the healthy cells. Early symptoms are insidious and often mimic those of common viral infections. As the leukemia progresses, symptoms become more pronounced and typically include

- unexplained low-grade FEVER
- general malaise or lethargy
- PAIN in the joints
- unintended weight loss
- sweating at night
- loss of APPETITE
- tiredness or fatigue
- easy bleeding or bruising, or the appearance of PETECHIAE (pinpoint hemorrhages beneath the SKIN)

The diagnostic path typically includes physical examination, diagnostic blood tests, and bone marrow biopsy. The physical examination may reveal SPLENOMEGALY (swollen SPLEEN) and LYMPHADENOPATHY (swollen lymph nodes). Characteristic patterns of abnormal cell counts and structures identify the different types of leukemia. In addition to abnormalities in the leukocytes, depletion of erythrocytes and platelets is common. Bone marrow biopsy confirms the diagnosis. Specialized laboratory tests, such as cytologic examination and immunophenotyping, establish the characteristics of the abnormal cells to identify the type of leukemia.

Treatment Options and Outlook

Treatment regimens for leukemia vary with the type of leukemia, the person's age, and the person's general health status aside from the leukemia. Chemotherapy and RADIATION THERAPY,

separately or in combination, remain the mainstay of the therapeutic arsenal, with the objective being to establish remission (a state in which there is no evidence of the leukemia and all blood counts and blood cells are normal). Oncologists use several staging systems for leukemia to identify the kinds of cells, cell lineage, and cell counts.

Chemotherapy is the treatment of choice, with blood stem cell or BONE MARROW TRANSPLANTATION sometimes an option depending on the leukemia's characteristics and stage at the time of diagnosis. Research continues to produce new chemotherapy agents and new combinations of existing agents that appear more successful, though their ability to sustain remission over time remains unknown. The initial phase of chemotherapy typically involves cycles of chemotherapy drugs administered over a period of one to two years, with maintenance oral chemotherapy drugs for another two and a half to three years for ALL. Oncologists may use radiation therapy to treat accumulations of cancerous lymphocytes in the BRAIN, spleen, and lymph nodes such as may occur with ALL. Many people need supplemental BLOOD TRANSFUSION and ANTIBIOTIC MEDICATIONS during chemotherapy.

CHEMOTHERAPY DRUGS USED TO TREAT LEUKEMIA

2-chlorodeoxyadenosine	5-azacytidine
6-thioguanine	anthracycline
arsenic trioxide	calicheamicin
carboplatin	hlorambucil
cladribine	conjugated MONOCLONAL ANTIBODIES (MABS)
cyclophosphamide	cytarabine
daunorubicin	dexamethasone
daunorubicin	fludarabine
hydroxyurea	idarubicin
ifosfamide	imatinib
interferon	L-asparaginase
melphalan	mercaptopurine
methotrexate	mitoxantrone
pentostatin	prednisolone
prednisone	teniposide
topotecan	vindesine
vincristine	

Across all types of leukemia, about 65 percent of people achieve initial remission with treatment. The rate of sustained remission (five years or longer) is much higher with acute than with chronic forms of leukemia, and in younger (under age 14 years) than older (over age 60) people. For children under age 14 who undergo treatment for ALL, about 80 percent achieve long-term remission such that doctors consider them cured of the leukemia. About 30 percent of adults who have ALL achieve similar long-term remission. Because successful treatment regimens are relatively new, however, doctors do not know what potential health complications, if any, may arise decades after treatment. Long-term survival rates are higher for lymphocytic leukemias than for myeloid leukemias.

Risk Factors and Preventive Measures

The causes of leukemia remain mostly unknown. Doctors do know that about 60 percent of people who have myelodysplasia syndrome eventually develop AML. As well, people who have first-degree relatives (parent, sibling, or child) who acquire ALL are about four times more likely to develop ALL themselves. Researchers have identified a number of potential risk factors associated with leukemia, though the extent and nature of the associations remains unclear. Among them are

- exposure to high-DOSE radiation, including radiation therapy
- previous chemotherapy for other kinds of cancer
- exposure to the industrial chemicals benzene and formaldehyde and their derivative compounds
- cigarette smoking
- infection with human T-cell leukemia virus 1 (HTLV-1)
- DOWN SYNDROME and CHROMOSOMAL DISORDERS that run in families

Most people who develop leukemia do not have any history of exposure to suspected risk factors, however, making prevention recommendations difficult. There are no known methods for preventing leukemia.

See also B-CELL LYMPHOCYTE; CANCER TREATMENT OPTIONS AND DECISIONS; ENVIRONMENTAL HAZARD EXPOSURE; ERYTHROPOIETIN (EPO); LYMPHOMA; MULTIPLE

MYELOMA; SIGNS AND SYMPTOMS OF CANCER; SMOKING AND HEALTH; STAGING AND GRADING OF CANCER.

leukocyte A white BLOOD cell, also referred to as a WBC. Leukocytes are the foundation of the body's IMMUNE RESPONSE and are phagocytic—that is, they have the ability to consume other cells. They circulate in the blood and the LYMPH as well as reside in tissues throughout the body. There are three basic types of leukocytes: granulocytes, monocytes, and lymphocytes. Each type has several subtypes. The SPLEEN and lymph tissues produce monocytes and lymphocytes; the red BONE MARROW produces granulocytes.

HEALTH CONDITIONS THAT AFFECT LEUKOCYTE COUNTS

ALLERGY response	ASTHMA
AUTOIMMUNE DISORDERS	CHEMOTHERAPY
environmental toxin exposure	HYPERSENSITIVITY REACTION
INFECTION	INFLAMMATION
LEUKEMIA	LEUKOPENIA
LYMPHOCYTOPENIA	LYMPHOMA
many cancers	medication side effects
MONONUCLEOSIS, INFECTIOUS	RADIATION THERAPY
surgery	vitamin B_{12} deficiency

A healthy adult has between 5,000 and 10,000 leukocytes per microliter of blood, with granulocytes accounting for about 70 percent. Increases in certain subtypes of leukocytes suggest particular health conditions. A substantial increase overall in LEUKOCYTE count may indicate a cancer of the bone marrow such as LEUKEMIA or LYMPHOMA. The ratio between erythrocytes (red blood cells) and leukocytes in the blood is also an important diagnostic indicator.

For further discussion of leukocytes within the context of blood and lymph structure and function please see the overview section "The Blood and Lymph."

See also B-CELL LYMPHOCYTE; CELL STRUCTURE AND FUNCTION; ERYTHROCYTE; HEMATOPOIESIS; PHAGOCYTOSIS; PLASMA; PLATELET; SIDE EFFECT; THYMUS.

leukopenia A decline in the number of leukocytes (white BLOOD cells) circulating in the blood to fewer than 4,000 leukocytes per microliter of whole blood. The most common manifestation of leukopenia is NEUTROPENIA, a shortage of granulocytes called neutrophils. Most leukopenia is secondary to other health conditions a person may have, such as viral infections or cancers that involve the BONE MARROW, and circumstances, such as CHEMOTHERAPY. Numerous medications can cause leukopenia as an undesired SIDE EFFECT of treatment. In such situations the doctor will evaluate the relative value of the inherent risks in continuing or discontinuing the causative medication. Leukopenia lowers the body's ability to resist and fight INFECTION and when severe can allow life-threatening infections to invade. Frequent or unusual infections, especially persistent GINGIVITIS or periodontitis, may suggest leukopenia. Treatment targets any infection or other underlying cause.

See also LYMPHOCYTOPENIA; PERIODONTAL DISEASE; THROMBOCYTOPENIA.

LEUKOCYTES

Type of Leukocyte	Subtypes	Organ that Produces
granulocytes	basophils, eosinophils, neutrophils	red BONE MARROW
monocytes	macrophages (reside in the tissues)	SPLEEN, lymph nodes
lymphocytes	T-cell lymphocytes	SPLEEN, lymph nodes, THYMUS
	cytotoxic T-cells	
	helper T-cells	
	memory T-cells	
	suppressor T-cells	
	B-cell lymphocytes	
	memory B-cells	
	PLASMA cells	

lymph The fluid that circulates through the LYMPH VESSELS. Lymph is clear and colorless or white with fat, depending on its location. It contains about 90 percent water and carries proteins, globulins, GLUCOSE, electrolytes, and other chemicals dissolved within it. Leukocytes, primarily lymphocytes and monocytes, circulate in the lymph, suspended in the fluid. Lymph originates from and returns to the BLOOD. Fluid from the blood (PLASMA) seeps from the capillaries into the spaces between the cells. This interstitial fluid carries the NUTRIENTS from the blood, surrounding the cells in a bath from which they withdraw the nutrients they need. Leukocytes in the blood move freely between the lymph and the blood. Lymph capillaries draw the interstitial fluid back into the lymph vessels, which carry the lymph they collect through a network of lymph vessels. Ultimately the lymph vessels return the lymph to the blood via its portals into the right and left subclavian veins.

Compared to the blood the HEART pumps through the circulation, the lymph moves leisurely through its network of vessels, achieving a top rate of about 100 milliliters an hour in the major trunk vessels (the lymphatic ducts). It flows primarily as a function of gravity, with some help from the massaging actions of contracting skeletal muscles during movement. Because most of the body's INFECTION-fighting action takes place in the lymph nodes and other lymph tissues, the lymph is the primary pathway for transporting pathogens for destruction by macrophages and other leukocytes in the lymph nodes. The lymph also is the primary channel for the body to carry the residue of infection to other structures and systems that eliminate it from the body (through phagocytosis as well as other means). CANCER cells can overload the lymph, hijacking it to become the pathway for their spread (METASTASIS) to other organs and parts of the body.

For further discussion of the lymph within the context of blood and lymph structure and function please see the overview section "The Blood and Lymph."

See also CISTERNA CHYLI; LYMPH NODE; RIGHT LYMPHATIC DUCT; THORACIC DUCT.

lymphadenitis INFLAMMATION or INFECTION of LYMPH nodes. Lymphadenitis characterizes systemic infections such as infectious mononucleosis and regional infections such as SEXUALLY TRANSMITTED DISEASES (STDS). It may affect any lymph nodes in the body though is most noticeable when it affects LYMPH NODE clusters near the surface of the SKIN, such as in the neck, axillae (underarms), and groin (inguinal). The typical symptoms of lymphadenitis are palpable lymph nodes that may range in size from that of a small pea to that of a large marble. The swellings are often painful, and the skin above the area may be reddened (erythematous) and warm to the touch when infection of the lymph nodes themselves is the cause. Diagnosis may require lymph node biopsy when there are no clear signs of infection or when lymphadenitis continues beyond six weeks.

Lymphadenitis without signs of infection may indicate cancer, either affecting the lymph structures (LYMPHOMA) or in METASTASIS from any location in the body. Pathogens or cancer cells traveling through the lymph can initiate such a massive activation of phagocytic response that the resulting action of macrophages and lymphocytes overwhelms the lymph nodes with cellular debris faster than the lymph can carry it away.

See also LYMPH VESSELS; MONONUCLEAR PHAGOCYTE SYSTEM; MONONUCLEOSIS, INFECTIOUS; PHAGOCYTOSIS.

lymphadenopathy Swelling and enlargement of the LYMPH nodes. Lymphadenopathy indicates that the affected lymph nodes are fighting an INFECTION in nearby tissues, and the enlargement is most often benign and normal. A common manifestation of lymphadenopathy is swollen lymph nodes in the neck when a person has a sore THROAT, or under the arm when there is a cut or bruise on the hand or arm. The swollen lymph nodes typically feel firm to the touch and may hurt. As the underlying infection improves, the swelling retreats, and the lymph nodes return to normal size. When lymph nodes throughout the body are swollen, the underlying cause is likely a systemic infection such as a VIRUS. Occasionally persistent lymphadenopathy suggests LYMPHOMA or LEUKEMIA, cancers of the lymph tissues or BONE MARROW.

See also LYMPHADENITIS; LYMPH NODE.

lymphangioma A noncancerous LESION made up of LYMPH VESSELS. Pathologically, doctors classify a

lymphangioma as hamartomatous, (harmartomas are benign tumors) which refers to the lesion's pattern of self-limiting growth. Lymphangiomas are congenital or arise soon after birth, most commonly manifesting as SKIN lesions on the head, back, arms, and legs, though the lesions may involve any external or internal epithelial tissue (skin and mucous membranes). Lymphangiomas grow slowly, then stop growing and remain the same size. Though not cancerous, a lymphangioma may cause problems or symptoms because of its location and size. A lymphangioma in the SMALL INTESTINE, for example, may interfere with the absorption of NUTRIENTS or create an ILEUS (obstruction).

Lymphangiomas that do not cause symptoms do not require treatment as they are self-limiting. A surgeon can operate to remove a lymphangioma that causes symptoms or is cosmetically unsatisfactory. However, the structure of a lymphangioma has no capsule and tends to diffusely infiltrate tissue, making it difficult for the surgeon to remove it completely. If the lymphangioma has not finished growing, it will recur. Most lymphangiomas are benign in that they do not cause symptoms or health problems.

See also BIRTHMARK; HEMANGIOMA.

lymphedema Swelling and often discomfort arising from inadequate LYMPH drainage and flow that allows interstitial fluid (fluid between the cells) to accumulate. Lymphedema most often occurs when INFECTION or CANCER that extensively engages the lymphatic system, or when surgery disrupts the LYMPH VESSELS and lymph nodes. Lymphedema is a common consequence of surgery and RADIATION THERAPY as treatments for cancer. Surgeons typically remove adjacent or sentinel lymph nodes, which are most likely to be affected by the cancer, during surgery to remove cancerous tumors to determine the extent to which the cancer has penetrated the tissues or metastasized (spread) to other tissues. Lymphedema can be debilitating when the swelling becomes substantial. Recurrent, progressive lymphedema often develops into fibrosclerosis (scarring and hardening) of the involved tissues.

It is important to distinguish lymphedema from other causes of swelling, such as edema (simple fluid retention) and ASCITES, because though the appearance of the affected area may be similar the treatment approaches differ. In chronic lymphedema the SKIN over the swollen area acquires a characteristic "orange peel" texture, which indicates damage to the underlying tissue. Tissue in the damaged area becomes susceptible to infection and ulceration, as the lymphedema compromises its BLOOD circulation and immune response. While conventional edema improves with diuretic medications, lymphedema does not.

For lymphedema, treatment focuses on improving the flow of fluid into and through the lymph vessels. Compression sleeves and stockings provide gentle, consistent pressure against the affected arm or leg, helping prevent interstitial fluid from accumulating. Some people with severe lymphedema benefit from compression pump therapy, in which a pump gently inflates and deflates pressure cuffs wrapped around the arms or legs, to help squeeze interstitial fluid into the lymph capillaries. Surgery to remove damaged portions of tissue and lymphatic structures is a treatment of end resort that may improve very severe lymphedema when other methods have failed, though itself can cause further or more extensive damage.

Lymphedema is a lifelong concern for most people who develop it, regardless of its cause though particularly after extensive surgery that disrupts the lymphatic structures or in which the surgeon removes lymph nodes. Many people can manage their symptoms and discomfort through preventive measures such as frequent movement or self-massage of involved areas and prompt therapeutic response when swelling begins.

See also HEART FAILURE; LYMPH NODE; SENTINEL LYMPH NODE DISSECTION; SURGERY BENEFIT AND RISK ASSESSMENT.

lymph node A small structure of lymphatic tissue. LYMPH nodes, sometimes erroneously called lymph glands, occur individually as well as in beadlike strings within the tissues. The lymph nodes range in size from that of a grain of rice to that of a kidney bean, and appear roughly kidney shaped.

Each lymph node contains high numbers of lymphocytes and macrophages (tissue-resident monocytes), which filter pathogens and cellular

debris from the lymph. Follicles within the lymph node contain B-cells and T-cells, which proliferate and mature in the follicles. The B-cells produce antibodies specific to the antigens the lymph carries into the lymph node. The lymph node adds these antibodies to the lymph as the lymph exits the node. The lymph node's follicles release additional T-cells as necessary to fight INFECTION, responding to chemicals PHAGOCYTOSIS releases. Extensive networks of lymphatic capillaries carry lymph among the lymph nodes as well as to and from the larger LYMPH VESSELS.

Lymph nodes commonly swell when they are actively responding to infection because they fill with the pathogenic cells they filter from the lymph, a circumstance doctors call LYMPHADENOPATHY. LYMPHADENITIS occurs when the infection involves the lymph node itself. The lymph nodes also can become seeding sites for cancer cells that are metastasizing (spreading) to other parts of the body. Most operations to remove cancerous tumors also include removal of adjacent lymph nodes to examine them for the presence of cancer cells, which is key to the STAGING AND GRADING OF CANCER.

See also ANTIBODY; ANTIGEN; LYMPHEDEMA; METASTASIS; PATHOGEN; SENTINEL LYMPH NODE DISSECTION.

lymphocyte A type of LEUKOCYTE (white BLOOD cell) that primarily resides in the LYMPH and lymph tissues. Lymphocytes are the body's primary immune defense and move through the lymph in response to antigens and pathogens. When more rapid deployment is necessary, lymphocytes enter the bloodstream. About 1 percent of the body's lymphocyte population circulates in the blood, making up about 25 percent of the circulating leukocytes. There are two major types of lymphocytes—T-cells and B-cells—and natural killer cells. Each type has different immune responsibilities.

T-Cells

T-cells, which make up about 75 percent of lymphocytes, originate in the BONE MARROW and migrate to the THYMUS to come to maturity. In the thymus T-cells acquire the ability to distinguish between "self" and "nonself," an essential function of determining whether the particles the T-cells encounter are invaders. Mature T-cells carry kinds of antibodies, identified as CLUSTERS OF DIFFERENTIATION, that denote the T-cell's immune function. There are numerous subtypes of T-cells, the most common being

- helper T-cells, which secrete a cytokine called CD4 (for cluster of differentiation 4) that directs the response of other T-cells
- cytotoxic T-cells, which attack invading cells by releasing chemicals that penetrate their cell membranes, which causes them to rupture and die
- suppressor T-cells, which reign in the IMMUNE RESPONSE after the immune attack has squelched the threat
- memory T-cells, which retain the ability to produce antibodies against the same ANTIGEN should it reappear in the body

B-Cells

B-cells, which make up about 10 percent of lymphocytes, originate in the bone marrow and migrate to the lymph tissues to come to maturity and await activation via contact with an antigen. When such contact occurs, the individual B-cell develops antibodies specific to the antigen, differentiates into either a memory B-cell or a PLASMA cell and then proliferates within the lymph tissues, lymph, and bloodstream. Memory cells "remember" the specific antigen and produce antibodies whenever the antigen again enters the body. This process provides long-term protection against pathogens. Plasma cells generate copious antibodies as they replicate, providing an immediate immune response to the PATHOGEN.

Natural Killer Cells

Natural killer (NK) cells are specialized lymphocytes that attack and destroy self cells that have become defective in some way. Researchers believe one function of NK cells is to attack tumors as they are beginning to develop, preventing them from taking root. NK cells also appear to attack cells that viruses hijack, preventing the VIRUS from replicating and causing infection.

For further discussion of lymphocytes within the context of blood and lymph structure and function please see the overview section "The Blood and Lymph."

See also B-CELL LYMPHOCYTE; CELL STRUCTURE AND FUNCTION; GRANULOCYTE; HEMATOPOIESIS; LYMPHOMA; MONOCYTE; MULTIPLE MYELOMA; NATURAL KILLER (NK) CELL; THYMECTOMY.

lymphocytopenia A decline in the number of lymphocytes in the BLOOD to fewer than 1,000 lymphocytes per microliter of whole blood. Lymphocytes circulate in the blood and the LYMPH, their primary role being to identify and attack invading pathogens to prevent and fight INFECTION. Lymphocytopenia often accompanies IMMUNODEFICIENCY disorders, notably HIV/AIDS (in which it may be one of the earliest indications of infection), infections such as TUBERCULOSIS and HEPATIS, and AUTOIMMUNE DISORDERS such as SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) and MYASTHENIA GRAVIS. Other causes include RADIATION THERAPY as cancer treatment, long-term PUVA (psoralen plus ultraviolet light of A wavelength) PHOTOTHERAPY for treatment of PSORIASIS, severe stress, and medications such as CORTICOSTEROID MEDICATIONS. Lymphocytopenia may be transitory, with the LYMPHOCYTE level returning to normal when the underlying cause improves. Depending on the cause, people who have lymphocytopenia may show few symptoms. Treatment targets the underlying condition. The health consequences of lymphocytopenia vary with the overall status of the IMMUNE SYSTEM.

See also LEUKOPENIA; NEUTROPENIA; THROMBOCYTOPENIA.

lymphoma A type of CANCER that affects the hematopoietic functions of the LYMPH system that results in the uncontrolled proliferation of lymphocytes, the type of LEUKOCYTE (white BLOOD cell) that the lymph tissues primarily produce. The lymphocytes congregate in the lymph tissues to form tumors.

LYMPHOMA VS. LEUKEMIA

LEUKEMIA and LYMPHOMA are both cancers that can affect the lymphocytes. However, leukemia is a CANCER of the BONE MARROW that alters the development and proliferation of lymphocytes that enter the BLOOD circulation. Lymphoma is a cancer of the lymphatic tissues that produce lymphocytes.

Though there are nearly three dozen identified types of lymphoma doctors assign them to one of two major categories, Hodgkin's lymphoma and non-Hodgkin's lymphoma. Doctors diagnose about 60,000 people with lymphoma in the United States each year. Lymphoma is the fifth most common kind of cancer among American adults and the third most common kind of cancer among children.

How Lymphoma Develops

Lymphomas originate in the reticuloendothelial or clone cells in the lymph structures that produce lymphocytes, notably the lymph nodes and the SPLEEN. Most lymphomas affect B-cell lymphocytes (B-cells) though some affect T-cell lymphocytes (T-cells). Hodgkin's lymphoma involves a specific kind of B-cell called a Reed-Sternberg cell. In all lymphomas, the affected lymphocytes proliferate and migrate to lymph tissues, such as lymph nodes and the spleen. The lymphocytes cluster into tumorous formations that drain the NUTRIENTS and other resources healthy cells require, causing the healthy cells to die and allowing the cancerous lymphocytes to continue proliferating.

A key marker for the extent and severity of lymphoma is whether tumors are present on only one side or on both sides of the DIAPHRAGM. Lymphomas present only on one side of the diaphragm (either above or below) tend to be less aggressive than those that are present in LYMPH NODE regions on both sides of the diaphragm, as well as more responsive to treatment (particularly those above the diaphragm). Cancerous lymphocytes can also metastasize to other kinds of tissues throughout the body, primarily traveling through the lymphatic system. The most common sites for lymphoma METASTASIS outside the lymphatic system are the BRAIN, SKIN, BONE, and BONE MARROW. However, because the lymphatic network extends throughout the interstitial tissues, metastases in advanced disease can appear anywhere.

Hodgkin's Lymphoma

Hodgkin's lymphoma, also called Hodgkin's disease, accounts for about 15 percent of diagnosed lymphomas. It most commonly affects people between ages 16 to 34 and over age 55. The presence of specifically abnormal B-cells, Reed-Sternberg cells, is the hallmark of Hodgkin's lymphoma.

There are five identified subtypes of Hodgkin's lymphoma:

- lymphocyte-predominant (also called nodular lymphocyte predominance)
- nodular sclerosis
- lymphocyte-rich (also called classical)
- mixed cellularity
- lymphocyte-depleted

Treatment regimens and prognoses differ for each subtype. Nodular sclerosis Hodgkin's lymphoma is the most common subtype, accounting for about two thirds of diagnoses, and tends to be moderately progressive. Lymphocyte-predominant Hodgkin's lymphoma tends to progress slowly; lymphocyte-depleted Hodgkin's lymphoma tends to be quite aggressive with rapid progression and frequent metastasis to organs outside the lymphatic system. In general, the higher the number of Reed-Sternberg cells, the more aggressive the cancer.

Non-Hodgkin's Lymphoma

The non-Hodgkin's lymphomas account for about 85 percent of diagnosed lymphoma and most commonly affect people over age 60, though can develop at any age. There are several dozen subtypes of non-Hodgkin's lymphoma, currently classified according to the type of tumor (also called a neoplasm) and its characteristics. Doctors further classify non-Hodgkin's lymphomas as to whether they are aggressive (rapidly growing)—high or intermediate grade—or indolent (slow growing)—low grade.

NON-HODGKIN'S LYMPHOMA SUBTYPES

AIDS-related	anaplastic large cell
angioimmunoblastic	blastic natural killer (NK)
BONE	Burkitt's
CENTRAL NERVOUS SYSTEM (CNS)	cutaneous T-cell
diffuse large cell	diffuse small noncleaved cell
eyelid	follicular
immunoblastic	lymphoblastic
lymphoplasmacytic	mantle cell
marginal zone	MUCOSA-ASSOCIATED LYMPHOID
mycosis fungoides	TISSUE (MALT)
nodal marginal zone	nasal NK/T
small lymphocytic	ocular (EYE)
splenic marginal zone	

Symptoms and Diagnostic Path

Many people do not have symptoms of lymphoma at the time of diagnosis. Rather, the doctor detects characteristic abnormalities in diagnostic blood tests conducted for other reasons, often as part of a ROUTINE MEDICAL EXAMINATION. When symptoms are present they can be vague and generalized, typical of common viral infections though they tend to persist or recur rather than resolving. Such symptoms may include

- painless swellings in the lymph nodes, most noticeable in the axillae (underarms), neck, or groin (LYMPHADENOPATHY)
- unexplained, frequent fevers
- unintended or unexplained weight loss
- profuse sweating at night
- tiredness, fatigue, or lethargy
- unexplained, generalized itching (PRURITUS)

The diagnostic path begins with the doctor's physical examination, which may reveal SPLENOMEGALY (enlarged spleen) or detect enlarged lymph nodes beneath the collarbone or in the abdomen. Diagnostic blood tests and bone marrow biopsy demonstrate the proliferation of lymphocytes. Other diagnostic procedures the oncologist may conduct include tissue biopsy of swellings, COMPUTED TOMOGRAPHY (CT) SCAN or MAGNETIC RESONANCE IMAGING (MRI) to detect the presence of tumors deep within the body, POSITRON EMISSION TOMOGRAPHY (PET) SCAN to examine the lymphatic network, and specialized immunocytology tests to determine the subtype of lymphoma. Based on the diagnostic findings the oncologist assesses the status of the lymphoma, assigning it a stage classification. Oncologists further designate a grade for non-Hodgkin's lymphoma that characterizes the level of aggressiveness. These assessments determine the appropriate treatment regimens and help valuate the prognosis (likelihood of REMISSION and survival).

Treatment Options and Outlook

Treatment regimens depend on the subtype, stage, and for non-Hodgkin's lymphomas the grade of the cancer as well as the person's age and overall health status. The typical treatment approaches, often administered in combinations, include

LYMPHOMA STAGING (HODGKIN'S AND NON-HODGKIN'S)

Stage	Characteristics
stage 1	early disease involves only a single LYMPH NODE region
stage 2	locally advanced disease involves two or more lymph node regions on one side of the DIAPHRAGM
stage 3	advanced disease involves two or more lymph node regions on both sides of the diaphragm
stage 4	widely disseminated disease involves multiple lymph node regions and METASTASIS to other organs such as the BONE or BRAIN
A	no symptoms at time of diagnosis (asymptomatic)
B	symptoms present at time of diagnosis
E	lymphoma is present in an organ outside the lymphatic system with no lymph node involvement

- RADIATION THERAPY, either above the diaphragm only (mantle field radiation) or from the neck to the pelvis (total nodal irradiation)
- CHEMOTHERAPY
- IMMUNOTHERAPY, also called biological response modifier therapy, including monoclonal antibody (MAb) therapy
- BONE MARROW TRANSPLANTATION and peripheral blood stem cell transplantation (PBSCT)
- watchful waiting for indolent (slow-growing and asymptomatic) lymphomas

Treatment results in at least one remission for most kinds of lymphoma. Many people experience extended remissions with few recurrences, and some people experience such long-term remissions as to have the oncologist consider the lymphoma cured. Other lymphomas are more resistant to treatment. Some chemotherapy drugs are effective as single agents, though more commonly oncologists prescribe chemotherapy drugs in combinations that target specific types of lymphoma. Many treatment regimens are cycles that repeat over several months to a year. Numerous complications resulting from treatment may occur, and vary with the treatment regimen, type and stage of lymphoma, and person's age and general health status.

CHEMOTHERAPY DRUGS USED TO TREAT LYMPHOMA

5-fluorouracil	bleomycin
carmustine	chlorambucil
cisplatin	cyclophosphamide
cytarabine	dexamethasone
doxorubicin	etoposide
fludarabine	fluoxymesterone
hydroxydaunomycin	ifosfamide
melphalan	methotrexate
mitoxantrone	pentostatin
prednisone	prednisone
procarbazine	rituximab
tositumomab	vincristine

Risk Factors and Preventive Measures

Researchers do not know what causes lymphoma, though a number of environmental factors appear to increase the risk for developing these forms of cancer. The most significant risk is for people who receive IMMUNOSUPPRESSIVE THERAPY after ORGAN TRANSPLANTATION, who are 100 times more likely to develop non-Hodgkin's lymphoma. Other suspected risk factors include

- HIV/AIDS
- INFECTION with human T-lymphocytic virus 1 (HTLV-1), EPSTEIN-BARR VIRUS, or human herpesvirus 8 (HHV-8)
- infection with *HELICOBACTER PYLORI*, the BACTERIA believed responsible for STOMACH CANCER
- occupational exposure to benzene
- occupational exposure to agricultural pesticides and herbicides, notably organophosphates and chlorophenols
- first-degree relatives (parents, siblings, children) who have lymphoma
- chromosomal TRANSLOCATION and other abnormalities

However, researchers do not know the extent to which these factors influence the development of lymphoma. Many people who develop lymphoma have no history of exposure to these factors, and far more people than not who have exposure do not develop lymphoma. Reducing or eliminating exposure to environmental toxins, treating infections such as *H. pylori,* and maintaining nutritious EATING HABITS can improve health overall. Otherwise, there are no known measures to prevent lymphoma.

See also AMYLOIDOSIS; B-CELL LYMPHOCYTE; CANCER RISK FACTORS; CANCER TREATMENT OPTIONS AND DECISIONS; ENVIRONMENTAL HAZARD EXPOSURE; ERYTHROPOIETIN (EPO); LEUKEMIA; LIFESTYLE AND HEALTH; MULTIPLE MYELOMA; NATURAL KILLER (NK) CELL; SIGNS AND SYMPTOMS OF CANCER; SMOKING AND HEALTH; STAGING AND GRADING OF CANCER.

lymph vessels An extensive network of channels that collect and circulate LYMPH, a watery fluid containing immune cells and substances as well as pathogens cleansed from the BLOOD and tissues. The lymph vessels, also called lymphatics, are similar in structure to the capillaries and veins of the cardiovascular system but have thinner walls. The lymph vessels carry lymph from the tissues through the lymph nodes, where lymphocytes neutralize or kill and macrophages consume pathogens, then deliver the cleansed fluid to the blood.

The smallest of the lymph vessels are the lymphatic capillaries, which arise from cul-de-sac structures within the interstitial fluid (fluid between the cells) in the tissues surrounding the CAPILLARY BEDS of the cardiovascular system. The shingled, single-cell walls of the lymphatic capillaries are permeable, allowing fluid to seep inside though preventing it from seeping back out. The lymphatic capillaries merge into the afferent lymphatics, somewhat larger lymph vessels that carry the lymph among the lymph nodes. The lymphatic capillaries in the SMALL INTESTINE, called lacteals, are uniquely able to absorb the fatty products of digestion, which they ultimately deliver to the blood.

The larger lymph vessels are not permeable and contain valves to keep lymph moving in only one direction, toward the central body. Their pathways roughly parallel those of the cardiovascular circulatory structures. In the central trunk region the lymph vessels merge into three reservoir-like structures. These structures are the

- CISTERNA CHYLI, which collects lymph from the lacteals and the abdominal lymph vessels
- THORACIC DUCT, which collects lymph from the cisterna chyli and the upper left body
- RIGHT LYMPHATIC DUCT, which collects lymph from the upper right body and head

The thoracic duct parallels the AORTA and drains into the left subclavian vein. The right lymphatic duct drains into the right subclavian vein. The lymph then becomes part of the blood.

For further discussion of lymph vessels within the context of blood and lymph structure and function please see the overview section "The Blood and Lymph."

See also LYMPHADENITIS; LYMPHEDEMA; LYMPH NODE; SENTINEL LYMPH NODE DISSECTION.

M–N

megakaryocyte See BONE MARROW.

methemoglobinemia A BLOOD oxygenation disorder in which methemoglobin, a structure of HEMOGLOBIN molecules that prevents iron from binding with oxygen, accumulates in the BLOOD. The result is diminished or insufficient oxygen delivery to the body's cells. Methemoglobin represents excessive iron molecule structures that are in a ferric state, in which they are unable to bind with oxygen. Normal iron molecules in the hemoglobin are ferrous. Methemoglobin forms naturally in the blood as a process of oxidation (cellular METABOLISM), though an enzyme system that converts ferric iron to ferrous iron continuously restores methemoglobin to hemoglobin. Methemoglobin is normally present in the blood in minute quantities, accounting for less than 1 percent of the total hemoglobin forms. Levels above 10 percent begin to cause symptoms, and levels above 70 percent are fatal.

A potential cause of methemoglobinemia is the illicit use of "nitrite poppers," inhaled isobutyl nitrite, butyl nitrite, and amyl nitrate products that are popular among some recreational DRUG users.

Methemoglobinemia most commonly results from toxic exposure to oxidizing chemicals or drugs. Dozens of industrial chemicals can cause methemoglobinemia, as can numerous medications in the nitrate, chlorate, and sulfonamide families of drugs, as well as topical anesthetics such as benzocaine and lidocaine. Exposure is usually chronic. Other causes of methemoglobinemia include hemoglobin disorders that allow excessive methemoglobin formulation and abnormalities in the blood enzyme system that normally removes methemoglobin from the blood.

Symptoms and Diagnostic Path

Symptoms of methemoglobinemia may mimic those of ANEMIA, such as fatigue and shortness of breath (DYSPNEA) especially with exertion or exercise, though important differences are present to help distinguish methemoglobinemia from other hemoglobin disorders. The most significant is a characteristic CYANOSIS that gives the SKIN a bluish brown color and does not improve with the administration of OXYGEN THERAPY. Blood tests that analyze hemoglobin composition determine the amount of methemoglobinemia in the blood; levels higher than 1 or 2 percent confirm the diagnosis though most people who show symptoms have much higher levels.

Treatment Options and Outlook

Most often, removing exposure to the causative substance allows the blood to recover on its own, usually within 72 hours. The doctor may choose to hospitalize the person until hemoglobin levels return to normal, to make sure the person receives adequate oxygenation. When symptoms are severe or persist, treatment may include methylene blue, a chemical that converts the hemoglobin's iron from ferric to ferrous. The typical therapeutic approach is to administer an intravenous injection of methylene blue to rapidly convert enough methemoglobin to hemoglobin to relieve symptoms, then switch to oral methylene blue until hemoglobin returns to normal. Rarely, a person who is having severe symptoms may require hyperbaric treatment, in which oxygen under pressure can enter the body through the skin to deliver oxygen to the tissues. Hyperbaric

therapy may also be appropriate for people who cannot take methylene blue.

Recovery is generally complete when the cause is toxic exposure. Genetic disorders of the hemoglobin or the enzyme mechanisms that regulate the balance between methemoglobin and hemoglobin may result in chronic methemoglobinemia and consequently the need for ongoing treatment (such as oral methylene blue) to prevent toxic accumulations.

Risk Factors and Preventive Measures

The most common cause of methemoglobinemia is toxic exposure to substances that cause oxidation, which overwhelms the body's normal mechanisms for managing cell metabolism. Avoiding chemicals, including drugs, that may cause methemoglobinemia is not simple, as they number in the dozens and include such commonly used medications as nitrates (cardiovascular) and topical anesthetics. People who have genetic disorders that interfere with hemoglobin production and function have increased risk for methemoglobinemia and should make every effort to avoid known causative agents.

See also ENVIRONMENTAL HAZARD EXPOSURE; G6PD DEFICIENCY; OCCUPATIONAL HEALTH AND SAFETY; OXYGEN–CARBON DIOXIDE EXCHANGE; SICKLE CELL DISEASE.

monocyte A LEUKOCYTE (white BLOOD cell), also called an agranulocyte, that has a single-lobed nucleus and contains no granules in its cytoplasm. The BONE MARROW and the LYMPH nodes produce monocytes, which have a two-phase existence in the body. During the first phase, the monocyte circulates in the blood and the lymph, functioning as a PHAGOCYTE that consumes pathogenic particles in the circulation. After about 24 hours the monocyte migrates into the tissue to enter its second phase of life. Once in the tissue the monocyte matures, becoming a fixed phagocytic cell called a macrophage that may acquire a specific name, depending on its location. About half of the body's macrophages migrate to the lymphatic structures. Most of the remainder reside in the LIVER, where they are called Kupffer cells. Macrophages that settle in the layers of the SKIN are Langerhans cells, and those that inhabit the BONE are osteoclasts.

Two to 8 percent of the body's leukocytes are monocytes; a normal monocyte count is 200 to 1100 monocytes per microliter of whole blood. The number of monocytes in circulation may increase with INFECTION, LEUKEMIA, LYMPHOMA, many other types of cancer, and AUTOIMMUNE DISORDERS in which there is active INFLAMMATION and autoimmune activity. The number of monocytes in circulation may decrease in aplastic ANEMIA and with steroid medications.

For further discussion of monocytes within the context of blood and lymph structure and function please see the overview section "The Blood and Lymph."

See also CELL STRUCTURE AND FUNCTION; ERYTHROCYTE; GRANULOCYTE; HEMATOPOIESIS; SKIN-ASSOCIATED LYMPHOID TISSUE (SALT).

multiple myeloma A CANCER of the BONE MARROW in which PLASMA cells, also called myeloma cells or myelocytes, proliferate, accumulating as lesions (growths) to develop within the BONE marrow cavities of the bones. The lesions prevent normal functioning of the bone marrow. They also damage bone tissue and weaken the bone structure. Plasma cells derive from lymphocytes that migrate to the bone marrow. Their function is to produce immune antibodies, or immunoglobulins, that are essential for the body's IMMUNE RESPONSE. They generally make up less than 5 percent of the cells in the bone marrow. In multiple myeloma plasma cells make up 10 percent or more of the bone marrow's cells. The cancerous plasma cells of multiple myeloma overproduce certain immune antibodies called monoclonal proteins or M-proteins. M-proteins alter the ways in which immunoglobulins bind with B-cell lymphocytes in the blood, reducing their ability to fight INFECTION.

The M-proteins also activate specialized phagocytic cells in the bone, called osteoclasts, accelerating the deconstruction phase of bone remodeling (the process through which bone tissue continuously replenishes). Osteoclastic activity releases excessive calcium into the bloodstream, affecting numerous body systems, including cardiovascular function and renal (kidney) function. The KIDNEYS produce ERYTHROPOIETIN (EPO), the HORMONE that stimulates the bone marrow to produce erythrocytes (red blood cells). Damage to the kidneys

such as occurs with multiple myeloma reduces EPO production, resulting in moderate to significant ANEMIA. M-proteins can bind with erythrocytes in the blood, further reducing their ability to transport oxygen. M-proteins can also bind with other substances in the blood including hormones and cells such as platelets. M-protein binding with platelets results in COAGULATION (clotting) abnormalities including excessive bleeding or thrombosis (clot formation within the blood vessels).

In the late 1990s researchers achieved a significant breakthrough in identifying the possible causes of multiple myeloma with the discovery of a connection between multiple myeloma and certain infections, notably herpesvirus type 8 (which causes another cancer, KAPOSI'S SARCOMA) and HEPATITIS C. As well, doctors have long noted connections between multiple myeloma and occupational exposure to pesticides (notably DDT) and petroleum products, and to radiation exposure such as RADIATION THERAPY. Multiple myeloma is more common in people over age 55 and accounts for 1 percent of all cancers doctors diagnose in the United States each year. It is more common in men than women and affects twice as many African Americans, though researchers are unsure of the reasons.

Symptoms and Diagnostic Path

About half of people diagnosed with multiple myeloma have no symptoms at the time of diagnosis, when blood tests performed for other reasons reveal the abnormalities consistent with multiple myeloma. Blood tests early in the course of the cancer may produce inconsistent and nonspecific findings that become relevant with subsequent diagnostic procedures. When symptoms are present they may include

- fatigue, especially with exertion
- frequent nosebleeds (EPISTAXIS) or easy bruising
- GASTROINTESTINAL BLEEDING
- PAIN, often in the back or that feels as though it originates in the bones
- excessive thirst
- HEADACHE
- a haze over the field of vision

Diagnostic blood tests typically show elevated blood calcium levels, altered blood cell counts, increased blood proteins, increased blood volume, the presence of M-proteins, and the presence of myelocytes (PLASMA cells) in the blood circulation. NEUTROPENIA and anemia are often present. Diagnostic imaging such as X-rays, COMPUTED TOMOGRAPHY (CT) SCAN, POSITRON EMISSION TOMOGRAPHY (PET) SCAN, and MAGNETIC RESONANCE IMAGING (MRI) allow the oncologist to assess the extent of bone involvement and damage. Bone marrow biopsy reveals high plasma cell counts and abnormal bone marrow structure.

Treatment Options and Outlook

CHEMOTHERAPY is the treatment of choice for multiple myeloma. The first chemotherapy agent developed to treat multiple myeloma in 1958, melphalan, remains the first line DRUG of choice today, commonly given in combination with prednisone, a corticosteroid medication. Oncologists use other chemotherapy agents, usually in combinations with each other and with CORTICOSTEROID MEDICATIONS, to tailor treatment regimens to an individual's age and the cancer's presentation, other health considerations, and preferences. Initial treatment typically produces REMISSION, though RECURRENCE within two years is common. Some people benefit from radiation therapy that targets myeloma lesions within the bones. New treatments continue to emerge as researchers gain understanding of the mechanisms of multiple myeloma.

DRUGS USED TO TREAT MULTIPLE MYELOMA

bortezomib	busulfan
carmusine	cisplatin
cyclophosphamide	dexamethasone
doxorubicin	etoposide
melphalan	prednisone
thalidomide	vincristine

Thalidomide and thalidomide analogs Thalidomide, which debuted in the 1950s as a treatment for MORNING SICKNESS and insomnia in PREGNANCY and quickly gained notoriety for causing BIRTH DEFECTS, emerged in the late 1990s as a successful treatment in some people for multiple myeloma that resists other therapies. Thalidomide sup-

presses the maturation of lymphocytes to plasma cells. Thalidomide analogs (such as Revimid and Actimid) are drugs closely related in chemical structure to thalidomide. Oncologists may administer thalidomide in combination with prednisone or dexamethasone, corticosteroid medications that help suppress bone marrow activity to slow the production of cancerous plasma cells.

Proteasome inhibitors In 2003 the US Food and Drug Administration (FDA) approved the proteasome inhibitor bortezomib (Velcade) for people who have experienced two relapses following conventional treatment approaches. Proteasome inhibitors block the actions of enzymes within cells that are crucial to the cell's ability to divide (reproduce). Clinical studies continue to investigate the effectiveness of these drugs, which appear to cause fewer side effects than conventional chemotherapy, as first-choice treatment.

Bone marrow and stem cell transplantation Autologous BONE MARROW TRANSPLANTATION or STEM CELL transplantation (self-transplantation with harvested cells), achieves remission in many people. For autologous transplantation, the oncologist harvests peripheral BLOOD STEM CELLS (PBSC) or stem cells from healthy areas of bone marrow; administers high-DOSE chemotherapy after cell harvesting to kill the cancerous bone marrow; and administers the harvested bone marrow or stem cells, which then grow to replace the cancerous bone marrow. Allogeneic stem cell transplantation, which uses stem cells from a tissue-matched donor, carries relatively high risks of complications including transplant rejection, infection, and other reactions, but is so far the only hope for a cure of multiple myeloma. Nonmyeloablative (the patient's bone marrow is not destroyed) allogeneic stem cell transplantation reduces the high risks of high-dose chemotherapy. Though not curative it may offer increased survival time.

Adjunctive therapies Oncologists use various medications to mediate the side effects of treatment as well as the complications that arise as the course of the cancer progresses. Among them are:

- Statins (such as Lipitor and Mevacor) counters the osteoclastic (bone destruction) stimulation M-proteins generate. Researchers discovered in the early 2000s that the statin medications used to treat HYPERLIPIDEMIA (elevated blood cholesterol and blood lipid levels) additionally stimulate osteoblastic (bone construction) activity, resulting in increased production of new bone tissue.
- Therapeutic EPO supplementation (Procrit) stimulates bone marrow production of erythrocytes, relieving anemia.
- Bisphosphonates bind to damaged bone cells and so prevent further osteoclastic action (destruction). This allows the body's natural bone remodeling mechanisms to repair the damage and rebuild the bone. However, bisphosphonates present the potential for serious kidney damage.
- ANTIBIOTIC MEDICATIONS aggressively treat the infections that become increasingly common as dysfunction of the IMMUNE SYSTEM progresses.

Lifestyle factors Because multiple myeloma affects bone remodeling, daily weight-bearing exercise such as walking is important to stimulate the body's normal osteoblastic (bone-constructing) mechanisms. These mechanisms further help bone tissue retain calcium, reducing the amounts of calcium that leaches into the circulation. Drinking lots of water to maintain high HYDRATION is also especially important. Staying well hydrated helps offset the tendency of the blood to become hyperviscous (thickened) as a consequence of the changes in its constitution that take place with the multiple myeloma. It also helps protect the kidneys by lowering the concentration of calcium and M-proteins that they must filter from the blood and pass in the URINE. Nutritious EATING HABITS provide the body with the NUTRIENTS it needs to maintain the best health status possible.

Risk Factors and Preventive Measures

Though environmental exposure, notably to pesticides and radiation, appears to play a role in the development of multiple myeloma, researchers do not know the mechanisms of such exposure. Many people who develop multiple myeloma do not have a known history of exposure to substances so far linked with an increased risk for this form of cancer, making it difficult for health

experts to recommend effective preventive measures.

Potential complications of both the multiple myeloma and its treatments present risks that affect the course of the cancer as well as the prognosis (outlook). M-proteins bind with numerous cell types, causing deposits to accumulate. Such deposits on NERVE cells tend to cause NEUROPATHY (pain or insensitivity). Such deposits within organs, such as the LIVER and the kidneys, may adversely affect their functions. Kidney damage may result in kidney failure and the need for dialysis. As well, chemotherapy agents and high-dose corticosteroids, standards of treatment for multiple myeloma, present the potential for numerous adverse effects. Most people who have multiple myeloma experience several periods of remission ranging from six months to two years in duration with each course of treatment.

See also AMYLOIDOSIS; CANCER TREATMENT OPTIONS AND DECISIONS; IMMUNOGLOBULIN; LEUKEMIA; LYMPHOMA.

myelocyte See BONE MARROW.

myelodysplasia syndrome Different constellations of symptoms, all arising from dysfunction of the BONE MARROW and all leading to various cytopenias (low BLOOD cell counts). In myelodysplasia, also called preleukemia, the number of hematopoietic cells within the BONE marrow increases but the produced cells are disordered and often released to the BLOOD while they are immature. Myelodysplasia syndrome most commonly affects people over age 60. Doctors do not know what causes this syndrome though a significant percentage of people who develop myelodysplasia have had exposure to industrial chemicals (notably benzenes) or radiation. Children who develop myelodysplasia often have underlying genetic disorders such as DOWN SYNDROME.

Myelodysplasia may affect any of the blood cells, resulting in a sometimes confusing clinical picture of mixed symptoms such as bleeding (PLATELET involvement) in combination with ANEMIA (ERYTHROCYTE involvement) or with frequent infections (LEUKOCYTE involvement). The SPLEEN often becomes enlarged (SPLENOMEGALY) as it attempts to filter defective blood cells from the blood and activate its hematopoietic functions to increase blood cell production in compensation for the bone marrow's inability to meet the body's needs. In some people myelodysplasia syndrome progresses to chronic or acute LEUKEMIA. Examination of the blood cells in a blood sample and bone marrow biopsy allow the doctor to make the diagnosis. Treatment may include transfusions of the deficient blood components and ANTIBIOTIC MEDICATIONS as necessary to treat infections. The outlook depends primarily on the type of blood cells involved.

See also BLOOD TRANSFUSION; ENVIRONMENTAL HAZARD EXPOSURE; HEMATOPOIESIS; INFECTION; LYMPHOMA.

myelofibrosis A chronic, degenerative condition of the BONE MARROW in which fibrous tissue replaces the red BONE marrow. Researchers do not know what causes myelofibrosis, which typically develops in people between the ages of 50 and 70, but believe it is an autoimmune response from a single defective blood STEM CELL (called a clonal dysfunction). The IMMUNE SYSTEM fails to recognize the deformed cells and produces antibodies to attack them. Because all BLOOD cells originate from BLOOD STEM CELLS, the attacking antibodies cause extensive damage within the bone marrow. The body's efforts to repair this damage result in pervasive SCAR formation that progressively shuts down the bone marrow.

The most apparent consequence is severe ANEMIA, as 99 percent of the bone marrow's production is oxygen-bearing erythrocytes (red blood cells). The shortfall activates the body's reserve erythropoietic functions in the LIVER and the SPLEEN, which begin producing erythrocytes. However, these organs cannot meet the demand and so both begin to enlarge with the effort (HEPATOMEGALY and SPLENOMEGALY, respectively).

Symptoms of myelofibrosis include those of anemia as well as bone PAIN, easy bleeding, and low resistance to infection as a consequence of diminished LEUKOCYTE (white blood cell) production. Blood tests show a low ERYTHROCYTE count, often low leukocyte and PLATELET counts, and characteristic "tear drop" deformity of the erythrocytes. Bone marrow biopsy shows the infiltration of fibrous tissue.

Treatment targets boosting the blood's erythrocytes by BLOOD TRANSFUSION and ERYTHROPOIETIN (EPO)

supplementation to stimulate the remaining red bone marrow to increase its erythrocyte production (erythropoiesis). Occasionally CHEMOTHERAPY and RADIATION THERAPY to suppress bone marrow function, curtailing proliferation of the defective stem cells, slows the condition's progression. BONE MARROW TRANSPLANTATION is sometimes a viable option. The outlook for myelofibrosis is variable; treatment is not curative and ultimately the bone marrow fails completely. Occasionally myelofibrosis evolves into acute myeloid LEUKEMIA, a rapidly progressive type of cancer in which blast cells (immature leukocytes) take over the bone marrow.

See also POLYCYTHEMIA VERA; THROMBOCYTHEMIA; THROMBOCYTOPENIA.

neutropenia Lower than normal numbers of neutrophils circulating in the BLOOD. Neutrophils are the most abundant of the three subtypes of granulocytes; the GRANULOCYTE is a type of LEUKOCYTE (white blood cell). Neutropenia, which can be acute or chronic, results in increased susceptibility to bacterial and fungal (yeast) INFECTION. Severe neutropenia can leave the body virtually defenseless against such infection, as neutrophils are the front line of response to invading pathogenic microorganisms.

The causes of neutropenia are numerous. Among the most common are

- acute viral infections such as mononucleosis, CYTOMEGALOVIRUS (CMV), INFLUENZA, HIV/AIDS, and HEPATITIS
- AUTOIMMUNE DISORDERS
- cancers of the BONE MARROW such as LEUKEMIA and MULTIPLE MYELOMA
- LYMPHOMA
- Vitamin B_{12} deficiency
- long-term, chronic ALCOHOL consumption
- RADIATION THERAPY and CHEMOTHERAPY
- adverse DRUG reactions, notably with NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) and penicillin ANTIBIOTIC MEDICATIONS

Chronic neutropenia is common with chronic infections such as HIV/AIDS and with AUTOIMMUNE DISORDERS. The primary symptoms of neutropenia are typically those of the infection that is present. Diagnostic blood tests that show lowered numbers of neutropenia in the blood confirm the diagnosis. Treatment targets the underlying health condition or removes the offending medication. In many people neutropenia is transient and self-limiting.

See also LEUKOPENIA; LYMPHOCYTOPENIA; MONONUCLEOSIS; INFECTIONS; THROMBOCYTOPENIA.

neutrophil See GRANULOCYTE.

P

phagocyte A white BLOOD cell (LEUKOCYTE) that consumes pathogens during an IMMUNE RESPONSE called PHAGOCYTOSIS. Granulocytes, and in particular neutrophils, are the primary phagocytes in the circulating blood. Macrophages are phagocytes that reside primarily in the LYMPH structures and the tissues. Protein markers on the surface of the PATHOGEN, called opsonins, attract phagocytes to the pathogen's location. The phagocyte extends its wall to encircle the pathogen, then releases enzymes that digest the pathogen. An individual phagocyte may digest up to a dozen pathogenic particles during the course of its existence.

See also BACTERIA; CELL STRUCTURE AND FUNCTION; MONONUCLEAR PHAGOCYTE SYSTEM.

phagocytosis The process through which a PHAGOCYTE (a specialized LEUKOCYTE) consumes a PATHOGEN or other cellular particle. Phagocytosis is a key defense mechanism of the body's IMMUNE RESPONSE and may take place in the BLOOD, primarily the domain of granulocytes (neutrophils and eosinophils), and in the tissues, primarily the realm of tissue-based monocytes (macrophages). When a pathogen invades the body, the immune response sends substances called opsonins to coat its surface. This process, called opsonization, marks the pathogen, attracting phagocytes. The most common opsonins are antibodies and the proteins the complement system produces.

The blood and the LYMPH carry phagocytes to the sites of opsonized pathogens. When the phagocyte reaches the pathogen it extends its cell wall to enclose the pathogen within its cytoplasm. Once enclosure is complete the phagocyte releases enzymes called lysozymes that digest the pathogen, breaking it down into its molecular components which the cell then recycles or releases as metabolic waste. The primary blood-based phagocytes are neutrophils, which respond to pathogens, and eosinophils, which respond to antigens. Monocytes circulate in the blood only for about 12 hours and then migrate into the tissues. Specialized phagocytes in the LIVER, the Kupffer cells, function in a somewhat cannibalistic manner, cleansing expired granulocytes from the circulating blood and recycling their molecular components into the bloodstream for other uses.

See also MONONUCLEAR PHAGOCYTE SYSTEM.

phlebotomy The clinical term for puncturing a VEIN with a sterile needle to withdraw BLOOD. Phlebotomy may be diagnostic, such as when drawing blood for diagnostic blood tests, or therapeutic, such as a treatment for HEMOCHROMATOSIS. Phlebotomy may be mildly uncomfortable, as the needle may sting as it penetrates the SKIN and the vein. The blood withdrawal itself is painless. The risks of phlebotomy are minor for most people and include mild bleeding, bruising, and discomfort at the puncture site.

See also BLOOD DONATION.

plasma The liquid portion of the BLOOD. Plasma is about 90 percent water and makes up 55 percent of the total blood volume. It contains numerous substances dissolved in it including electrolytes, hormones, enzymes, antibodies, GLUCOSE, and CLOTTING FACTORS (specialized proteins). It also carries the blood cells in suspension. Plasma is available for transfusion as a blood product, in fresh or fresh-frozen form. Plasma derivative products extracted from donated plasma include cryoprecipitated antihemophilic factor (AHF), ALBUMIN, IMMUNOGLOBULIN, and Rh immunoglobulin.

For further discussion of the plasma within the context of blood and lymph structure and function please see the overview section "The Blood and Lymph."

See also BLOOD TRANSFUSION; ERYTHROCYTE; HEMAPHERESIS; HORMONE; LEUKOCYTE; LYMPHOCYTE; MONOCYTE.

plasmapheresis See HEMAPHERESIS.

platelet The cellular structure indispensable for COAGULATION (clotting), also called a thrombocyte. Platelets, which are actually cell fragments rather than intact cells, separate from parent cells in the BONE MARROW called megakaryocytes, the largest cells in the BONE marrow. When platelets emerge into the circulation they become the smallest cell particles in the circulating blood. Their small size permits them to travel into any blood vessel, even the tiniest arterioles and venules, to respond to bleeding. Platelets lack nuclei and thus, like erythrocytes, cannot divide. They live in the circulation for about 10 days.

The normal number of platelets in the blood is 130,000 to 400,000 per cubic milliliter. The SPLEEN holds about 30 percent of the blood's platelets within its red pulp, releasing them into the circulation when needed to respond to bleeding. This containment helps reduce the risk for inadvertent agglutination as platelets swirl into contact with one another in the bloodstream.

Any breach in a blood vessel that allows blood to escape results in the release of the enzyme tissue factor (factor III), which attracts droves of platelets to the site. As the platelets agglutinate (come into contact with the damaged site and with one another) they release chemicals such as serotonin, thromboxane, and phospholipids that extend and focus the coagulation cascade.

For further discussion of platelets within the context of blood and lymph structure and function, please see the overview section "The Blood and Lymph."

See also ANTICOAGULATION THERAPY; ARTERY; CELL STRUCTURE AND FUNCTION; CLOTTING FACTORS; HEMAPHERESIS; VEIN.

platelet aggregation The process through which platelets respond to chemical signals in the BLOOD, allowing them to adhere to each other and to collagen fibers in the blood to form the hemostatic plug that will become a blood clot at the conclusion of the COAGULATION cascade. The formation of collagen and the conversion of fibrinogen (clotting factor I) to the enzyme fibrin together initiate a sequence of chemical conversions that alter PLATELET surface proteins as well as attract more platelets to the location of the injury. As the coagulation cascade continues, platelets accumulate. The platelets change shape, developing threadlike extensions called pseudopods that allow them to extend like vines into the weave of collagen fibers. The surface of the platelets continues to undergo chemical changes that attract fibrinogen and release arachidonic acid, which oxidizes to form PROSTAGLANDINS, short-acting hormones that are key players in the IMMUNE SYSTEM'S INFLAMMATION response. Prostaglandins further attract platelets to the site.

Converted CLOTTING FACTORS begin to weave fibers of protein among the fibers of fibrin, thrombin, and collagen, forming a netlike structure that entraps other cells flowing through the blood. When the clot reaches critical mass additional chemical reactions begin to shut down the coagulation cascade, bringing the clotting process to a halt. The surface proteins of circulating platelets revert, and the platelets no longer adhere to each other. The reversion also activates mechanisms within the platelets that cause them to contract, pulling them tightly into the clot structure. Other proteins cause the clot to harden, cementing it in place.

Inflammation of the ARTERY walls, such as occurs with CORONARY ARTERY DISEASE (CAD), attracts platelets in the same manner as do wounds, setting in motion the events of platelet aggregation in ways that are detrimental to health. Doctors often prescribe antiplatelet medications to slow platelet aggregation in people who have had HEART ATTACK OR STROKE, or who have CAD. Most of these medications work by blocking the oxidation of arachidonic acid, which then inhibits prostaglandin formation. The most commonly used antiplatelet medication is aspirin. Platelet aggregation can also occur as a SIDE EFFECT of medications or a dysfunction of coagulation.

See also ANTICOAGULATION THERAPY; ATHEROSCLEROTIC PLAQUE; C-REACTIVE PROTEIN.

polycythemia vera A myeloproliferative condition of the BLOOD in which the red BONE MARROW produces an excessive volume of erythrocytes (red blood cells), platelets, and neutrophils that results in increased cell volume and decreased fluid volume (PLASMA) in the blood. This myeloproliferation (overproduction by the bone marrow) thickens the blood (hyperviscosity), making it more difficult for the cardiovascular system to transport and increasing the risk for thrombosis (blood clots). As the myeloproliferation progresses, the marrow pushes immature, deformed, and defective cells into the blood that are unable to perform the normal functions of their cell types. Polycythemia vera is a chronic and potentially debilitating disorder most commonly diagnosed in people age 60 and older.

Symptoms and Diagnostic Path

Symptoms may not appear until the bone marrow dysfunction is considerably advanced and typically include

- tiredness and fatigue
- weakness
- HEADACHE
- lightheadedness
- easy bleeding or bruising
- PRURITUS (itching)
- SKIN flushing (redness), particularly of the face

The doctor's examination often reveals an enlarged SPLEEN (SPLENOMEGALY), a consequence of the overload on the spleen to remove defective erythrocytes from the circulating blood or to produce additional erythrocytes if those in circulation are too defective to adequately transport oxygen (ANEMIA). Some people also have an enlarged LIVER (HEPATOMEGALY), as the liver too has a role in cleansing dysfunctional erythrocytes from the blood. Diagnostic blood tests characteristically show elevated ERYTHROCYTE, neutrophil, and PLATELET counts, with the hematocrit (percentage of erythrocytes in the blood) greater than 54 percent in men or 49 percent in women. The doctor may also perform a bone marrow biopsy, which demonstrates clusters of megakaryocytes (the parent cells of platelets) and other characteristic alterations in the marrow's structure.

Treatment Options and Outlook

PHLEBOTOMY (therapeutic withdrawal of blood) is adequate treatment for many people who have polycythemia vera, particularly when the diagnosis comes early in the condition. The usual therapeutic approach is daily phlebotomy to remove 300 to 500 milliliters of blood until the hematocrit drops to 45 percent. Weekly to monthly phlebotomy sessions then may keep the condition in check.

When phlebotomy is not sufficient, substances to suppress bone marrow function, called myelosuppressive therapy, can put the condition in REMISSION for up to several years at a time. Myelosuppressive therapy has a high risk for causing acute myeloid LEUKEMIA, however, so current treatment protocols call for its use only in people over age 70.

The most significant and frequent complications of polycythemia vera are thrombosis (the formation of blood clots in the blood vessels), which can lead to HEART ATTACK or STROKE, and acute myeloid leukemia. Without treatment polycythemia vera is generally fatal within two years. With treatment, many people enjoy good QUALITY OF LIFE for 15 to 20 years beyond diagnosis.

Risk Factors and Preventive Measures

Because researchers do not know what causes polycythemia vera, there are no known preventive measures. The condition is uncommon, and more likely to occur in men than women. Polycythemia vera is unusual in a person under age 40. Early diagnosis and treatment improves quality of life and outlook.

See also HEMOCHROMATOSIS; MYELOFIBROSIS; THROMBOCYTHEMIA; THROMBOCYTOPENIA.

R–S

reticulocyte An ERYTHROCYTE (red BLOOD cell) that enters the blood's circulation from the BONE MARROW just before it has reached maturity. Reticulocytes are somewhat larger than erythrocytes and normally make up about 1 percent of the erythrocytes in circulation. A reticulocyte matures into an erythrocyte after being in circulation for about a day. Reticulocytes are still continuing to synthesize (make) HEMOGLOBIN, so contain somewhat less hemoglobin than mature erythrocytes.

An increased number of reticulocytes in circulation indicates the BONE marrow is producing erythrocytes more rapidly than normal. Accelerated erythropoiesis may suggest various underlying causes, such as undetected internal bleeding, hemolytic ANEMIA, and extended exposure to high altitude (which increases the body's need for oxygen). The reticulocyte count also rises in PREGNANCY and with some medications such as NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS), levodopa taken to treat PARKINSON'S DISEASE, and sulfonamide ANTIBIOTIC MEDICATIONS.

A decreased number of reticulocytes in circulation suggests chronic INFECTION, exposure to radiation, aplastic anemia, or iron-deficiency anemia. The reticulocyte count also may drop with CHEMOTHERAPY, the antibiotic chloramphenicol, and the immunosuppressant medication azathioprine typically taken after ORGAN TRANSPLANTATION to prevent organ rejection or severe RHEUMATOID ARTHRITIS.

For further discussion of reticulocytes within the context of blood and lymph structure and function please see the overview section "The Blood and Lymph."

See also CELL STRUCTURE AND FUNCTION; HEMATOPOIESIS; IMMUNOSUPPRESSIVE THERAPY.

Rhesus (Rh) blood type See BLOOD TYPE.

right lymphatic duct A major LYMPH VESSEL that collects LYMPH draining from the right upper body and head. The right lymphatic duct is about a quarter-inch in diameter and two inches long, adjacent to the subclavian VEIN beneath the clavicle (collarbone). It empties into the right subclavian vein, delivering lymph to the bloodstream.

For further discussion of the right lymphatic duct within the context of blood and lymph structure and function, please see the overview section "The Blood and Lymph."

See also CISTERNA CHYLI; THORACIC DUCT.

sickle cell disease An inherited genetic disorder of defective HEMOGLOBIN, a protein compound erythrocytes (red blood cells) contain that binds with oxygen. Though the primary effect of sickle cell disease, also called sickle cell ANEMIA, is anemia (insufficient oxygen in the blood), the condition also causes significant PAIN and damage to organs throughout the body. In the United States sickle cell disease is significantly more common in African Americans. Around the world, sickle cell disease is most common among people of African, northern Mediterranean, Indian, and Middle Eastern descent. About 70,000 Americans have sickle cell disease and another 2 million have sickle cell trait. Sickle cell disease is the most common inherited blood disorder.

Sickle cell disease gets its name from the characteristic sickle shape of the erythrocytes. The deformity results from the defective hemoglobin, called hemoglobin S, which the erythrocytes carry. When hemoglobin S releases oxygen during the OXYGEN-CARBON DIOXIDE EXCHANGE, it polymerizes—its structure undergoes molecular changes that cause its molecular weight to increase. This stiff-

ens and hardens the normally flexible erythrocytes, pulling them into a sickle or crescent shape.

The rigidity and inflexibility prevents the erythrocytes from folding and twisting as they pass through the small blood vessels, causing them to create blockages. The blockages cause swelling, pain, and eventually damage to organs and structures throughout the body. People who have sickle cell disease have very high risk for STROKE, HEART ATTACK, acute chest syndrome (blockages in the lungs that cause INFECTION), and loss of vision.

The changes also make the erythrocytes more fragile, and they easily break apart as the flow of blood jostles them around. Sickled erythrocytes die after only about 20 days in the blood circulation, whereas normal erythrocytes live for 90 to 120 days. The shortened lifespan further limits the ability of the blood to transport oxygen, establishing chronic anemia.

ADAPTIVE DEFECT

Researchers believe the gene mutation that causes sickle cell disease originated in the form of sickle cell trait as an adaptation to protect against malaria infection. The sickled erythrocytes resist the parasite that causes MALARIA. In sickle cell trait, the person has some hemoglobin S and mostly normal hemoglobin—an ideal blend for simultaneously maintaining health and thwarting malaria. The adaptation backfires only when two people with sickle cell trait conceive a child, at which time the recessive autosomal inheritance pattern of the mutated hemoglobin gene becomes a risk for passing on too much of a good thing to the child.

The inheritance pattern for sickle cell disease is autosomal recessive, which means both parents must pass the defective hemoglobin gene to their child. People who are carriers of the mutated hemoglobin gene have sickle cell trait, with one mutated and one normal hemoglobin gene. They have small amounts of hemoglobin S though mostly have normal hemoglobin and have no indications of sickle cell disease. However, their children may end up with sickle cell disease if they inherit the sickle cell mutation from each parent. When both parents have sickle cell trait, there is a 1 in 4 chance for the child to have sickle cell disease, a 2 in 4 chance the child will also be a carrier, and a 1 in 4 chance the child will inherit two normal genes.

Symptoms and Diagnostic Path

Symptoms generally begin to emerge when a child is about a year old. For the first year of life the child has an abundant supply of fetal hemoglobin, which has the ability to prevent polymerization of hemoglobin S. However, the child's own hemoglobin gradually replaces the fetal hemoglobin and this protection disappears, typically between age 6 months and 10 months. Early symptoms of sickle cell disease in a child are swollen hands and feet (sometimes called hand and foot syndrome), a consequence of damaged erythrocytes blocking the small blood vessels in the hands and feet to prevent blood from circulating out. Other symptoms include

- pain from blockages
- FEVER
- fatigue from anemia
- diminished vision from damage to the RETINA

People who have sickle cell disease may also have

- frequent infections resulting from damage to the SPLEEN and LYMPH tissues
- jaundice, yellow discoloration of the skin resulting from excessive bilirubin in the blood circulation as the components of the dead erythrocytes accumulate in the LIVER
- delayed growth due to severe anemia

A blood test can detect the presence of hemoglobin S, which affirms the diagnosis. In the United States, hospitals routinely run this test on all newborns. Examination of the erythrocytes under the microscope also shows the characteristic sickle shape.

Treatment Options and Outlook

Treatment for sickle cell disease may include ANALGESIC MEDICATIONS for pain relief, blood transfusions to replace the damaged erythrocytes with healthy erythrocytes (which is effective for the life cycle of the transfused erythrocytes), and the medication hydroxurea (which can reestablish fetal hemoglo-

bin production in some children). BONE MARROW TRANSPLANTATION is sometimes an option for people who have severe symptoms. There is no cure for sickle cell disease. Sickle cell trait does not produce symptoms or develop into sickle cell disease, so it requires no treatment. Many people who have sickle cell trait do not know it.

Risk Factors and Preventive Measures

Because sickle cell disease is an inherited genetic disorder, the only risk factor is heredity. It is a good idea for people who do not know their sickle cell status, especially African Americans, to have the blood test for hemoglobin S before conceiving children. GENETIC COUNSELING can help with family planning decisions when both parents have sickle cell trait.

See also BLOOD TRANSFUSION; HEMOLYSIS; PRIAPISM.

spleen A soft structure of lymphatic tissue located in the upper left abdomen to the left of the STOMACH and PANCREAS, behind the protective enclosure of the rib cage. Fibrous ligaments anchor the spleen to the stomach, COLON, and left kidney. The spleen holds about 300 milliliters of BLOOD, roughly 4 percent of the body's total blood supply, and contains about a third of the body's platelets (the cells responsible for COAGULATION). Its high blood content gives the spleen a dark red color and a somewhat porous texture. The spleen has two main structural and functional sections that filter the blood for different substances, the red pulp and the white pulp.

White Pulp

The white pulp consists of nodules and follicles, similar to those of other lymphatic tissues such as the LYMPH nodes, arranged in sheathlike structures that encase each of the tiny blood vessels (arterioles) within the spleen. The white pulp has two primary roles, to filter antigens from the circulating blood and to produce lymphocytes (a type of LEUKOCYTE). These functions are interrelated in that the lymphocytes bear antibodies specific to the antigens the white pulp traps. When the lymphocytes enter the circulation of the blood or lymph, their antibodies allow them to intercept and destroy pathogens such as viruses or BACTERIA that carry the antigens.

Red Pulp

The red pulp surrounds the white pulp. In the developing fetus the red pulp produces the majority of blood cells, erythrocytes (red blood cells) and leukocytes (white blood cells) alike, until about the fifth month of PREGNANCY, after which the red bone marrow takes over erythropoiesis (ERYTHROCYTE production). Hematopoietic capability of the red pulp remains available but dormant after birth. Throughout life, the red pulp serves as an extramedullary (out of the marrow) resource that the body can press into action to produce erythrocytes.

The red pulp also filters the blood, culling outdated, defective, or damaged erythrocytes from circulation. Phagocytic cells called macrophages that reside within the red pulp break down the erythrocytes, sending components such as HEMOGLOBIN and BILIRUBIN back into the blood for transportation to the LIVER, which recycles them. The red pulp also filters other cellular debris from the blood.

Potential Health Conditions Involving the Spleen

The spleen's primary vulnerability is trauma, which can cause life-threatening hemorrhage (uncontrolled bleeding). A blow to the upper abdomen, such as may occur in MOTOR VEHICLE ACCIDENTS or with aggressive contact sports, can cause a rupture injury to the spleen. Such a blow also can fracture a rib, causing a penetrating wound to the spleen. SPLENECTOMY (surgical removal of the spleen) then becomes necessary. Though not essential for life, the spleen performs numerous functions vital to the IMMUNE RESPONSE and blood cell maintenance. Other lymphatic structures and the liver can partially compensate for the spleen's loss, though the risk for serious INFECTION significantly increases. There are many health conditions that can cause the spleen to enlarge (SPLENOMEGALY). The spleen also enlarges when fighting systemic infections such as infectious mononucleosis and in some cancers.

For further discussion of the spleen within the context of blood and lymph structure and function please see the overview section "The Blood and Lymph."

See also CANCER; LYMPH NODE; MONONUCLEAR PHAGOCYTE SYSTEM; MONONUCLEOSIS, INFECTIOUS; PHAGOCYTOSIS.

splenectomy A surgical OPERATION to remove the SPLEEN. Though the spleen performs many vital immune and BLOOD-related functions, it is not essential for life. Because the spleen contains 4 percent of the body's blood volume and a third of its platelets, it is vulnerable to life-threatening hemorrhage with trauma. Doctors may also choose to remove the spleen for therapeutic or prophylactic (preventive) reasons in conditions such as chronic myeloid LEUKEMIA and MYELOFIBROSIS.

Splenectomy may be an OPEN SURGERY or a laparoscopic surgery, depending on the reason and the person's overall health status, performed under general ANESTHESIA. Laparoscopic splenectomy, which involves removing the spleen using a lighted endoscope and small tools the surgeon inserts through four or five small incisions in the upper left abdomen, usually requires an overnight stay in the hospital with three to four weeks for full recuperation. Open splenectomy requires a single incision, four to five inches long, through which the surgeon opens the abdominal cavity and removes the spleen. The open surgery may require three to five days in the hospital with four to six weeks for full recovery.

COMMON REASONS FOR SPLENECTOMY

hemolytic ANEMIA	LEUKEMIA
LYMPHOMA	PORTAL HYPERTENSION
THROMBOCYTOPENIA	trauma with hemorrhage
uncontrolled SPLENOMEGALY	

As with any surgery, excessive bleeding and INFECTION are potential risks. Because absence of the spleen compromises the body's IMMUNE RESPONSE, lowered resistance to infection is a common consequence of splenectomy. Doctors recommend pneumococcal PNEUMONIA vaccination before splenectomy when possible and immediately after when splenectomy is an emergency surgery. The doctor may recommend other immunizations, depending on individual health circumstances. People who have had splenectomy must remain diligent in regard to potential infections, even those that are seemingly minor such as COLDS. Many doctors recommend ANTIBIOTIC PROPHYLAXIS (preventive ANTIBIOTIC MEDICATIONS) to offset the IMMUNE SYSTEM's diminished response.

See also SURGERY BENEFIT AND RISK ASSESSMENT.

splenomegaly An enlarged SPLEEN. Splenomegaly signals an underlying health condition and is not itself a disorder. The spleen is a structure of lymphatic tissue. One of its key roles is to remove old or damaged BLOOD cells from circulation. Many circumstances and health conditions that cause increased numbers of blood cells in the circulation can also cause splenomegaly. These range from systemic infections, such as infectious mononucleosis, to blood disorders, such as THROMBOCYTHEMIA, to cancers, such as LEUKEMIA and LYMPHOMA. Some people feel a sense of uncomfortable fullness with splenomegaly, though most people are unaware of the condition until a doctor detects it.

There is no specific treatment for splenomegaly; so treatment targets the underlying cause. Splenomegaly significant enough to extend the spleen beyond the protective boundary of the rib cage presents a risk for injury resulting in hemorrhage, as the spleen contains about 4 percent of the body's total blood volume and a third of its platelets (the cells responsible for clotting).

CONDITIONS IN WHICH SPLENOMEGALY MAY OCCUR

AMYLOIDOSIS	ANEMIA
CIRRHOSIS	congestive HEART FAILURE
HEPATITIS	leishmaniasis
LEUKEMIA	LEUKOPENIA
LYMPHOMA	MALARIA
MONONUCLEOSIS, INFECTIOUS	MULTIPLE MYELOMA
MYELOFIBROSIS	POLYCYTHEMIA VERA
PORTAL HYPERTENSION	psittacosis
SARCOIDOSIS	SICKLE CELL DISEASE
SYPHILIS	SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)
THALASSEMIA	THROMBOCYTHEMIA
THROMBOCYTOPENIA	TUBERCULOSIS

See also HEPATOMEGALY; SPLENECTOMY.

T

thalassemia A genetic disorder of the BLOOD in which the body fails to produce one or more of the proteins necessary for the synthesis of HEMOGLOBIN, the protein that enables erythrocytes (red blood cells) to carry oxygen. The consequence is ANEMIA (inadequate oxygen to the cells throughout the body). There are two basic types of thalassemia: alpha and beta, designated according to the responsible defunct protein chain. Within these types are a number of subtypes. In general, thalassemia is more common among people of Asian and African heritage (alpha thalassemia) or Mediterranean heritage (beta thalassemia).

Symptoms and Diagnostic Path

Mild thalassemia may produce no symptoms, while severe thalassemia can be life-threatening. Symptoms are generally similar for the major forms of thalassemia and are those of anemia. They may include

- chronic fatigue
- weakness
- HEADACHE
- Shortness of breath, especially with exertion or exercise
- PALPITATIONS

Severe symptoms may involve cardiovascular crisis such as HEART ATTACK. Some forms of thalassemia include excessive iron absorption by the LIVER, HEART, and other organs, resulting in permanent damage such as CIRRHOSIS, LIVER FAILURE, and HEART FAILURE. Long-term thalassemia often results in significant SPLENOMEGALY (enlarged SPLEEN) and permanent changes in BONE structure that weaken the bones (notably with beta thalassemia). In some people the bone changes cause pathologic or spontaneous FRACTURE, which is the first indication of an underlying thalassemia.

The diagnostic path includes blood tests to measure serum iron levels, which are characteristically elevated in severe thalassemia but may be low in mild forms, and to assess hemoglobin composition by hemoglobin electrophoresis. BONE MARROW biopsy demonstrates the altered appearance of developing erythrocytes that characterizes thalassemia. X-rays can confirm changes to the structure of the bones, which are most apparent in the skull and the long bones of the arms and legs.

Treatment Options and Outlook

People who have symptoms as a result of their thalassemia require lifelong BLOOD TRANSFUSION, with either whole blood or packed red cells (erythrocytes), typically every two or three weeks. These transfusions provide normal erythrocytes that can transport oxygen through the bloodstream, with transfusions timed at intervals that approximate the body's normal process of new ERYTHROCYTE release and old erythrocyte cleansing. However, blood transfusions contribute to an escalation of iron accumulation that requires treatment, usually therapeutic CHELATION THERAPY (heavy metals detoxification).

Therapeutic SPLENECTOMY (removal of the spleen) can reduce symptoms when excessive HEMOLYSIS (acceleration of the body's normal process for destroying erythrocytes) contributes to symptoms by stimulating increased erythropoiesis (production of new erythrocytes). BONE MARROW TRANSPLANTATION may become a viable option when other treatment approaches fail to control symptoms and symptoms are severe.

Thalassemia is lifelong. Most people with alpha forms of thalassemia enjoy a good QUALITY OF LIFE,

aside from the intrusion of regular blood transfusions, and normal LIFE EXPECTANCY. Beta forms of thalassemia tend to be more severe and have a less optimistic outlook. The secondary HEMOCHROMATOSIS (iron accumulations in the tissues) can become a significant health factor itself, creating a therapeutic dilemma.

Risk Factors and Preventive Measures

Because thalassemia is genetic and inherited, the primary risk factors are family history and presence of the causative GENE mutations. Doctors advise GENETIC TESTING and GENETIC COUNSELING for people who have family history of thalassemia. It is possible for an individual to carry the gene defect and show no symptoms of the condition, which can result in passing the gene defect, and the disease, to the individual's children.

See also HEMATOPOIESIS; INHERITANCE PATTERNS; MUTATION; SICKLE CELL DISEASE.

thoracic duct The largest vessel of the lymphatic system. The thoracic duct collects LYMPH from the CISTERNA CHYLI and the left upper body, and drains into the left subclavian VEIN to deliver lymph to the bloodstream. About the diameter of a pencil, the thoracic duct extends from the cisterna chyli in the central trunk to base of the neck, a distance of about 16 inches, somewhat paralleling the AORTA. Like a vein, the thoracic duct has smooth-MUSCLE walls that rhythmically contract and contains valves to prevent its contents from backflowing. Muscular movement, such as occurs with physical activity or exercise, massages lymph through the thoracic duct toward the subclavian vein. Several branches of lymph vessels feed into the thoracic duct as it courses through the chest, rejoining to form a single segment that intersects with the subclavian vein beneath the clavicle (collarbone).

For further discussion of the thoracic duct within the context of BLOOD and lymph structure and function please see the overview section "The Blood and Lymph."

See also LYMPH NODE; LYMPH VESSELS; RIGHT LYMPHATIC DUCT.

thrombocyte See PLATELET.

thrombocythemia A condition of the BLOOD in which the body overproduces platelets (also called thrombocytes), resulting in dysfunctional COAGULATION. Thrombocythemia, also called thrombocytosis, is a myeloproliferative disorder that can be primary (an independently occurring disorder, also called essential or idiopathic thrombocythemia) or secondary (a consequence of other health conditions or SPLENECTOMY). Doctors do not know what causes primary thrombocythemia, which occurs most commonly in people over age 50.

COMMON CAUSES OF SECONDARY THROMBOCYTHEMIA

INFECTION	INFLAMMATORY BOWEL DISEASE (IBD)
iron deficiency ANEMIA	LYMPHOMA
RHEUMATOID ARTHRITIS	SARCOIDOSIS
TUBERCULOSIS	Wegener's granulomatosis

Symptoms and Diagnostic Path

The excess platelets in the blood cause disturbances of coagulation that often result in these symptoms, which may be subtle or overt:

- easy bleeding, notably from the mucous membranes, such as frequent nosebleeds (EPISTAXIS), or from the gastrointestinal tract
- easy bruising
- clotting (thrombosis)
- SPLENOMEGALY (enlarged SPLEEN)
- HEADACHE or dizziness
- hemorrhage

A blood PLATELET level higher than 500,000 platelets per microliter (mc/L) of blood typically confirms the diagnosis, though the doctor may choose to do a BONE MARROW biopsy. Bone marrow biopsy shows an abundance of megakaryocytes, the parent cells of platelets, oversize platelets, and platelet fragments.

Treatment Options and Outlook

Treatment for secondary thrombocythemia targets the underlying condition, with resolution of the thrombocythemia after improvement in that condition. Treatment for primary thrombocythemia aims to suppress myeloproliferation (bone marrow cell production activity). Common forms of myelosuppressive therapy are radioactive phos-

phate and the CHEMOTHERAPY agents hydroxyurea and anagrelide. Some people benefit from platelet apheresis, a form of HEMAPHERESIS that removes platelets from the blood and returns all other blood components to the person. The doctor will closely monitor the complete blood count (CBC) as well as platelet function and coagulation during treatment, usually with weekly blood tests.

Primary thrombocythemia is a chronic condition that requires ongoing treatment. Many people will remain relatively symptom-free once treatment stabilizes platelet production. The condition takes a more serious course in some people who may experience worsening symptoms, notably hemorrhage. Rarely, primary thrombocythemia evolves into chronic myeloid LEUKEMIA (CML), a cancer of the bone marrow.

Risk Factors and Preventive Measures

Because doctors do not know what causes primary thrombocythemia, risk factors remain unknown and there are no known preventive measures. Early diagnosis and appropriate treatment offer the most optimal prognosis (outlook) to minimize the level to which the condition affects QUALITY OF LIFE.

See also POLYCYTHEMIA VERA; THROMBOCYTOPENIA.

thrombocytopenia A disorder of the BLOOD in which the blood contains too few platelets (also called thrombocytes), the cells active in COAGULATION (clotting). Thrombocytopenia, also called thrombopenia, is a secondary condition that develops as a consequence of prolonged bleeding, aplastic ANEMIA, blood disorders such as THROMBOCYTHEMIA, and cancers affecting the BONE MARROW.

POTENTIAL CAUSES OF THROMBOCYTOPENIA

acute idiopathic thrombopenia purpura	ANTIDIABETIC MEDICATIONS
AUTOIMMUNE THROMBOCYTOPENIA	aplastic ANEMIA
chronic ALCOHOL consumption	BLOOD TRANSFUSION reaction
CIRRHOSIS	chronic idiopathic thrombopenia purpura
GASTROINTESTINAL BLEEDING	heparin
HIV/AIDS	LEUKEMIA
MYELOFIBROSIS	PLATELET dysfunction
quinidine	rifampin
SEPTICEMIA	sulfa ANTIBIOTIC MEDICATIONS

Certain medications may also cause thrombocytopenia as an undesired SIDE EFFECT. Thrombocytopenia may occur when the bone marrow cannot produce enough platelets or when the SPLEEN and LIVER remove too many platelets from the blood.

Symptoms and Diagnostic Path

The characteristic sign of thrombocytopenia, regardless of its underlying cause, is excessive superficial bleeding. Symptoms include

- PETECHIAE, pinpoint hemorrhages beneath the surface of the SKIN that have the appearance of a RASH
- ECCHYMOSIS, a pattern of easy and excessive bruising with minor bumps and scrapes
- unprovoked bleeding from the nose (EPISTAXIS), gums, URETHRA, and other mucous tissues
- blood in the urine, stool, or vomit
- excessive bleeding with dental procedures or surgery
- signs of intracranial bleeding (bleeding within the skull)

A blood test that shows the low PLATELET count with normal counts and appearance of other blood cells is fairly conclusive of the diagnosis, especially when an underlying condition known to cause thrombocytopenia also is present. The doctor may choose to do a bone marrow biopsy. Because thrombocytopenia can be an early indication of HIV INFECTION, the doctor is also likely to do an HIV antibodies test to determine whether HIV infection is present.

Treatment Options and Outlook

Treatment depends on the underlying condition. Sometimes platelet transfusions are necessary to provide enough platelets for proper coagulation. Thrombocytopenia is not usually a life-threatening condition and typically resolves when the underlying condition improves.

Risk Factors and Preventive Measures

The primary risk factors for thrombocytopenia are the conditions that result in its development. Avoiding these factors, such as alcohol consumption or a medication that is causing thrombocytopenia as a side effect, or treating the condition

dispenses the likelihood for developing thrombocytopenia.

See also DISSEMINATED INTRAVASCULAR COAGULATION (DIC); THROMBOCYTHEMIA.

thymectomy A surgical OPERATION, performed under general ANESTHESIA, to remove the THYMUS, a structure of lymphatic tissue located behind the sternum (breastbone) that produces T-cells. Tendrils of the thymus often extend upward toward the THYROID GLAND and downward over the HEART. The loose structure of the thymus can make it challenging to surgically remove.

Thymectomy is the treatment of choice for most cancers of the thymus, which are uncommon. Doctors sometimes use thymectomy to treat severe AUTOIMMUNE DISORDERS, such as MYASTHENIA GRAVIS, as a method to restrict the body's ability to produce T-cells and thus limit the IMMUNE RESPONSE. Thymectomy in childhood has extensive consequences for IMMUNE SYSTEM development though does not appear to alter IMMUNE RESPONSE in adults. Most people require only a one or two day stay in the hospital, and about four to six weeks for full recovery.

See also LYMPHOCYTE; SPLENECTOMY.

thymus A structure of lymphatic tissue located in the upper central chest, behind the sternum (breastbone) midway between top of the HEART and the sternal notch at the base of the THROAT. The thymus is fairly large at birth, spreading in a loosely shaped "H" across the great vessels that emerge from the heart. The tissue of the thymus sometimes extends upward to make contact with the THYROID GLAND and downward to drape over the heart's upper chambers, the atria. Occasionally fragments of thymic tissue exist as unattached, isolated lobules typically remaining in the upper chest and lower neck.

The thymus is most active in youth, serving as the incubator in which T-cells, the lymphocytes crucial for the body's defense against INFECTION, mature and differentiate (acquire their functional characteristics). The thymus typically enlarges as a child approaches PUBERTY, its peak time of activity, then begins to recede. By midlife little more than strands of thymic tissue remain. The thymus also produces hormones—key among them being thymosin, thymulin, thymopoietin, and thymocyte humoral factor—that regulate T-cell maturation.

STATUS LYMPHATICUS: "ENLARGED" THYMUS

In the 1940s and 1950s, conventional medical wisdom blamed the large thymus of childhood for unexplained sudden death in children, conveying upon the condition the diagnostic label *status lymphaticus*. RADIATION THERAPY to shrink the thymus became the prevailing treatment. By the 1960s doctors recognized the thymus was normally large in children and abandoned the diagnosis and its treatment.

Researchers believe the thymus has other functions related to IMMUNE RESPONSE, though remain unable to determine their precise mechanisms. An infant born without a thymus has no ability to develop an IMMUNE SYSTEM; this CONGENITAL ANOMALY is nearly always fatal in infancy. There also appears to be a correlation between the thymus and MYASTHENIA GRAVIS, an autoimmune disorder in which the immune system produces antibodies that target acetylcholine, the NEUROTRANSMITTER that facilitates NERVE signals traveling between nerve cells and MUSCLE cells. An enlarged thymus is common in people who have myasthenia gravis and removing it (THYMECTOMY) often results in dramatic improvement in the condition. The thymus may have a role in other AUTOIMMUNE DISORDERS such as SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) and GRAVES'S DISEASE. Thymoma and thymic CARCINOMA are two forms of cancer that may develop in the thymus. Cancer of the thymus is uncommon.

For further discussion of the thymus within the context of blood and lymph structure and function please see the overview section "The Blood and Lymph."

See also HIV/AIDS.

V

vitamin K A vitamin that is a crucial catalyst, or coenzyme, in the COAGULATION process (also called coagulation cascade). Vitamin K (naphthoquinone) plays a role in activating seven of the CLOTTING FACTORS in various stages of coagulation, helping convert them from the inactive state in which they circulate in the BLOOD to active proteins that form clots. Vitamin K also is important for new BONE growth and BONE DENSITY. The major forms of vitamin K are phylloquinone (K1), menaquinone (K2), and menadione (K3, synthetic and cannot be converted into K1).

DIETARY SOURCES OF VITAMIN K

Food	Amount of Vitamin K per 1-Cup Serving
Kale, cooked	1,062 micrograms (mcg)
spinach, cooked	888 mcg
collard greens	836 mcg
parsley	324 mcg
Brussels sprouts, cooked	219 mcg
onions, spring	207 mcg
broccoli, cooked	220 mcg
lettuce, leaf (Bibb, Boston)	167 mcg
asparagus, cooked	144 mcg
prunes, stewed	65 mcg
lettuce, romaine	57 mcg
peas, cooked	40 mcg
blackberries, blueberries (fresh)	28 mcg
lettuce, head (iceberg)	13 mcg
turkey, cooked	5 mcg
strawberries, raw	4 mcg

Source: USDA National Nutrient Database for Standard Reference, SR17 Nutrients List: Vitamin K (Phylloquinone)

Most of the vitamin K the body uses is in the form of phylloquinone and comes from plant foods in the diet, notably leafy green vegetables such as spinach, kale, and broccoli. Intestinal BACTERIA also synthesize (manufacture) a small amount of vitamin K (menaquinone). Though vitamin K is fat soluble, the body does not maintain a significant store of it. Consequently, health experts have established daily adequate intake values of 90 micrograms per day for women and 120 micrograms per day for men.

The commonly used oral anticoagulant medication, warfarin, inhibits clotting by blocking the actions of vitamin K. Doctors may recommend restricting consumption of foods high in vitamin K for those who are taking ANTICOAGULATION THERAPY or maintaining consistent consumption of vitamin K–containing foods (not to exceed the daily adequate intake value) so the body's levels of vitamin K remain stable.

Because infants often have inadequate levels of vitamin K in their blood at birth, most hospitals in the United States administer vitamin K supplement injections to newborns within 24 hours of birth, which is the current recommendation of the American Academy of Pediatrics. Doctors do not agree on the value or effectiveness of routine vitamin K supplements in other circumstances. Most health experts recommend obtaining the body's supply of vitamin K through dietary sources, which is fairly easy for most Americans to do because a wide variety of foods contain this nutrient. Menadione is the synthetic supplement form of vitamin K.

See also ANTICOAGULATION THERAPY; OSTEOPOROSIS; VITAMINS AND HEALTH.

von Willebrand's disease A hereditary, genetic bleeding disorder resulting from a deficiency or

molecular abnormality of clotting factor VIII. Unlike HEMOPHILIA A, which also results from clotting factor VIII deficiency, von Willebrand's disease affects both men and women equally. Its inheritance pattern is autosomal dominant, meaning a child can acquire the condition when only one parent has the defective GENE. Von Willebrand's disease is the most common bleeding disorder in the United States, affecting about 1 percent of the American population. The condition is mild in most people, though severe trauma or major surgery may cause life-threatening hemorrhage especially in people who do not know they have the disorder.

Symptoms and Diagnostic Path

The most common symptom of von Willebrand's disease is somewhat prolonged bleeding with cuts, wounds, dental procedures, and surgeries. Easy bruising, frequent nosebleeds (EPISTAXIS), and bleeding gums are also common symptoms. Some people may periodically develop PETECHIAE, pinpoint hemorrhages beneath the surface of the SKIN that have the appearance of a RASH. Women who have von Willebrand's disease may have unusually heavy menstrual bleeding. The diagnostic path includes blood tests to measure clotting times, PLATELET AGGREGATION, and the level of von Willebrand factor multimers in the blood. The results of these diagnostic blood tests are usually conclusive for the diagnosis.

Treatment Options and Outlook

No treatment is necessary for people who have mild symptoms, though anyone diagnosed with von Willebrand's disease should carry or wear identification that alerts emergency medical personnel to the condition. Treatment before scheduled surgeries or for bleeding due to trauma is administration of PLASMA cryoprecipitate, which contains concentrated CLOTTING FACTORS, or purified factor VIII concentrate.

People who have von Willebrand's disease should not take NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS), including aspirin, as these medications further decrease PLATELET AGGREGATION and increase bleeding.

Risk Factors and Preventive Measures

As von Willebrand's disease is hereditary, family history is the only known risk factor. People who have von Willebrand's disease may choose GENETIC COUNSELING before deciding to conceive children. Most people who have von Willebrand's disease experience little interference with QUALITY OF LIFE. The condition generally remains stable throughout life. Other health conditions that affect bleeding may result in a compound effect to produce more intense symptoms than either condition alone would otherwise manifest.

See also COAGULATION; GENETIC DISORDERS.

THE PULMONARY SYSTEM

The pulmonary system brings oxygen into the body and expels metabolic wastes in the form of gases. Physician specialists who treat conditions of the pulmonary system are internists who have subspecialty certifications in pulmonary medicine (pulmonologists). Physician specialists who operate on the LUNGS and related structures are thoracic surgeons. This section, "The Pulmonary System," presents an overview of the structures and functions of the pulmonary system, a discussion of pulmonary health and disorders, and entries about the health conditions that can affect the lungs and related structures.

Structures of the Pulmonary System

TRACHEA
BRONCHUS
bronchiole
ALVEOLUS
PLEURA
left lung
  upper lobe
  lingula (lingular segment)
  lower lobe
right lung
  upper lobe
  middle lobe
  lower lobe
DIAPHRAGM

Functions of the Pulmonary System

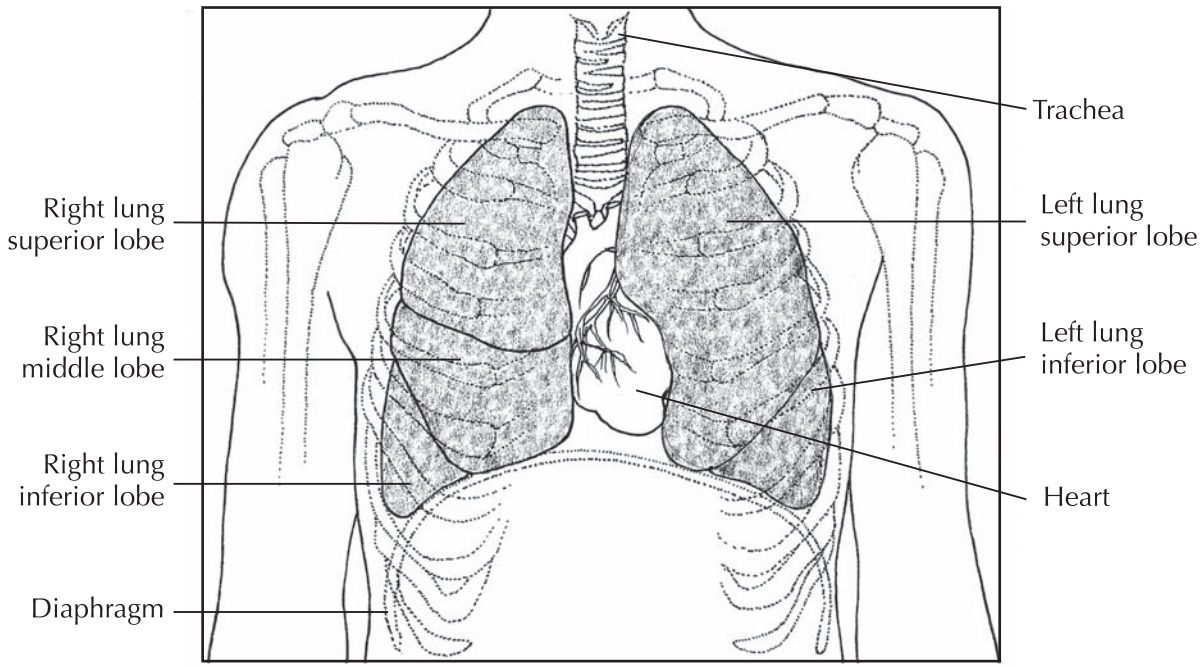
The LUNGS bring life-giving oxygen into the body and remove toxic gaseous wastes from it. An asymmetrical pair, these spongy structures rhythmically expand and compress about 15 to 20 times a minute. Expansion, or inhalation, draws air and oxygen into the lungs; compression, or exhalation, expels carbon dioxide and other gases that are metabolic waste byproducts of cellular activity. The structures of the nasal cavity and the upper airway (THROAT) bring air, containing about 21 percent oxygen, into the body. The NOSE and SINUSES warm and moisturize the air.

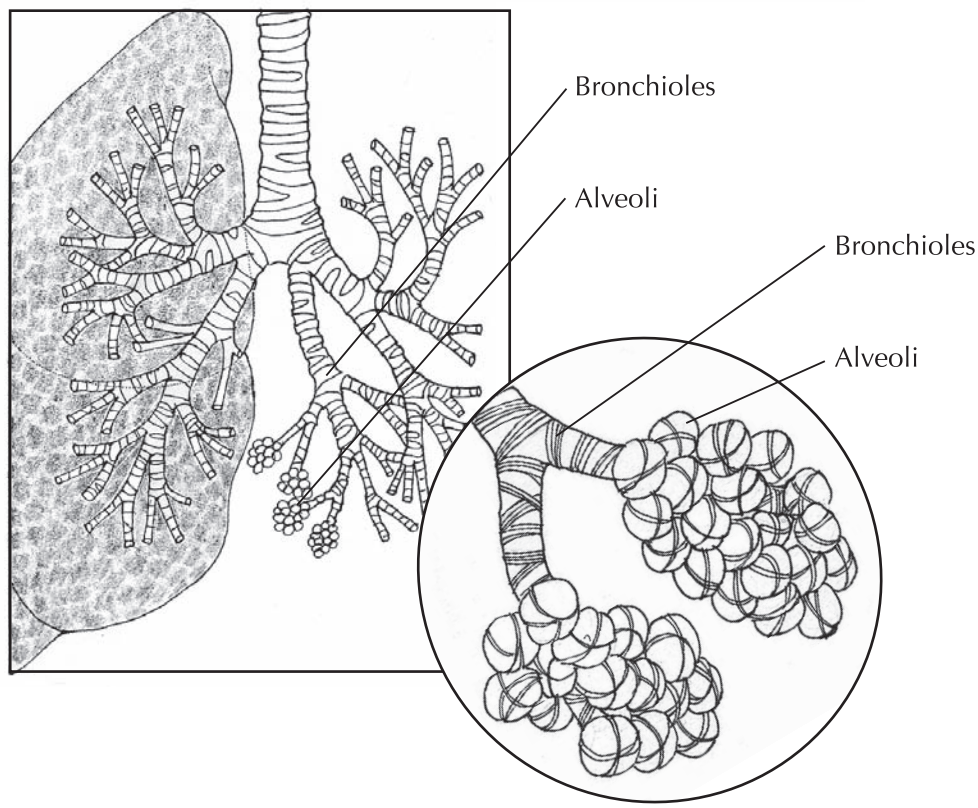
Carrying that air to the lungs are the TRACHEA, bronchi, and bronchioles—a branching structure of progressively smaller airways. The air's destination is the alveoli, tiny membranous sacs that cluster grapelike at the ends of the bronchioles. A webbing of capillaries (tiny blood vessels) surrounds each ALVEOLUS, carrying erythrocytes (red BLOOD cells) waiting to receive oxygen molecules and release carbon dioxide molecules. This process, the OXYGEN–CARBON DIOXIDE EXCHANGE, gives the body life.

LOBES AND SEGMENTS OF THE LUNGS

Right Lung	Left Lung
Right upper lobe	***Left upper lobe***
apical segment	apical-posterior segment
posterior segment	anterior segment
anterior segment	superior lingular segment (lingula)
Right middle lobe	inferior lingular segment (lingula)
lateral segment	***Left lower lobe***
medial segment	superior segment
Right lower lobe	anterior basal segment
superior segment	lateral basal segment
anterior basal segment	posterior basal segment
medial basal segment	
lateral basal segment	
posterior basal segment	

The lungs: asymmetry in synchronization The lungs fill the thoracic cavity from neck to DIAPHRAGM and sternum to spine. Though paired, the lungs differ somewhat in structure. The right lung is larger than the left lung, containing three lobes to the left lung's two. The left lung must accommodate the HEART, which nestles into an indentation called the cardiac notch. Some anatomists consider the small tail of tissue in the left lung that drops behind the heart, called the lingula, as a structure separate from either lobe of the left lung though most designate it a segment of the left upper lobe. Each lobe of the lung further contains structural divisions called bronchopulmonary segments, 10 among the three


Trachea
Right lung superior lobe
Left lung superior lobe
Right lung middle lobe
Left lung inferior lobe
Right lung inferior lobe
Heart
Diaphragm


Bronchioles
Alveoli
Bronchioles
Alveoli

lobes of the right lung and 8 among the two lobes of the left lung. A bronchial cluster—which includes bronchi, bronchioles, alveoli, blood vessels, LYMPH VESSELS, and nerves—branches into each segment.

The cells of the respiratory tract are primarily epithelial cells, the same kind of cells that make up the SKIN. The epithelial cells lining the trachea and bronchi contain cilia, tiny hairlike projections that sweep debris, such as dust and pollen, and excess mucus from the respiratory tract outward to the throat for coughs to expel them from the body. A tissue-thin membrane, the PLEURA, covers the outer surface of the lungs. The pleura secretes serous fluid to lubricate the lungs in their perpetual movement, protecting them from friction and irritation. Lung tissue is highly porous, with the substance of the lungs being about 15 percent solid tissue and 85 percent air and blood.

The heart pumps the body's full volume of blood—about five liters—through the lungs once each minute to pick up oxygen and release carbon dioxide. The blood, which flows through the lungs in a closed circuit from the heart via the PULMONARY ARTERIES and back to the heart via the PULMONARY VEINS, pulses through a dense, meshlike capillary network surrounding the alveoli. Pulmonary and cardiovascular mechanisms maintain an intricate balance between the flow of blood and the flow of air, with the blood flow constantly adjusting to flood into CAPILLARY BEDS surrounding alveoli that have strong air flow and recede from those with diminished air flow. This balance provides the greatest efficiency for getting oxygen into the bloodstream.

The bronchial tree: trachea, bronchi, bronchioles, and alveoli Like a hollow trunk, the trachea supports the treelike bronchial structure that brings air into the lungs. The trachea extends from the back of the throat about four and a half inches down to the midchest, where it branches into the right BRONCHUS and left bronchus. The spine in the back and the sternum in the front protect the trachea's path. The trachea's most vulnerable exposure is at the front of the neck, where it passes in front of the ESOPHAGUS before dropping behind the sternal notch. C-shaped bands of CARTILAGE help protect the trachea as well as give it the rigidity necessary to maintain an open passageway against ever-changing air pressures. Long fibers of smooth MUSCLE complete the posterior wall of the trachea.

The trachea terminates with the branching of the right main bronchus, going to the right lung, and left main bronchus, going to the left lung. Like the trachea, the bronchi contain smooth muscle with rings of cartilage for support and STRENGTH. The smooth muscle fibers of the trachea and the bronchi contract and expand in response to the air pressure changes of inhalation and exhalation. Each bronchus quickly divides to branch to the lung's lobes (lobular bronchi), and further subdivides into segmental bronchi, branching bronchi, and ultimately the very tiny and cartilage-free bronchioles. The alveoli cluster at the ends of the bronchioles.

The alveoli are the work stations of the lungs, and each lung contains about 150 million of them. Each microscopic alveolus looks like a small sac; an alveolar cluster contains dozens of alveoli that bubble from the end of a bronchiole. The alveolar membrane, the thickness of a single cell, forms the interface between the pulmonary system and the cardiovascular system, allowing the oxygen and carbon dioxide molecules to cross from the air within the lungs and the blood within the capillaries. Their bunched arrangement vastly extends the surface area available for oxygen exchange within the confined space of the chest. The total surface area of the alveoli, if spread out flat, is about the size of a tennis court.

Breathing: mechanics, physics, and molecular exchange The balance between oxygen and carbon dioxide in the blood regulates pulmonary respiration (BREATHING). As carbon dioxide from cellular METABOLISM accumulates in the blood, it reaches a threshold that triggers a sequence of biochemical signals to the brainstem. The brainstem then initiates a RESPIRATORY CYCLE, sending NERVE signals that trigger the diaphragm (the flat, broad muscle that forms the base of the thoracic cavity) and the intercostal muscles (the muscles between the ribs) to contract. In response the diaphragm flattens, pulling the floor of the thoracic cavity downward. The intercostal muscles simultaneously contract to pull the ribs outward and upward. The synchronized movements enlarge the thoracic cavity, drawing air into the lungs. When the diaphragm and the intercostal muscles

relax, the thoracic cavity returns to its resting size and the lungs expel air.

With each breath the EPIGLOTTIS, a flap of cartilaginous tissue at the back of the throat, opens and closes like a valve to allow air to pass in and out of the trachea and to keep other substances (such as saliva, food, and drink) from entering the trachea and lungs. With the changing of air pressure that occurs between inhalation and exhalation, oxygen molecules migrate through the micrometers-thin membrane walls of the alveoli into the blood circulating through the capillaries that surround the alveoli. Carbon dioxide molecules cross back in exchange. The respiratory cycle repeats about 20,000 times every 24 hours, varying in rate according to the body's oxygen needs.

ALTITUDE AND OXYGEN

Though the *percentage* of oxygen in the air remains constant regardless of altitude, the *concentration* of oxygen molecules decreases as altitude increases. The concentration of oxygen molecules in the air is greater at sea level than in the mountains. At a higher altitude the LUNGS must work harder to extract enough oxygen to meet the body's needs. In the short term the body compensates by raising the RESPIRATION RATE—breathing faster. After about 72 hours at a higher altitude, the decreased concentration of oxygen in the air stimulates the BONE MARROW to produce more erythrocytes (red BLOOD cells), which increases the blood's capacity to carry oxygen.

Health and Disorders of the Pulmonary System

The lungs rhythmically pull air into and release air from the body in a choreography the BRAIN coordinates with the HEART RATE and BLOOD PRESSURE to maintain the vital supply of oxygen to tissues throughout the body. Aerobic conditioning through regular physical exercise, not smoking, and maintaining healthy weight are among the key factors that keep the lungs functioning efficiently across the span of life.

Lung capacity peaks during the 20s and gradually declines with increasing age. People who remain aerobically fit continue to have strong pulmonary function despite this decline, as their lungs still have enough reserve to meet the body's needs. People whose lifestyles are sedentary are more likely to experience a decline in lung capacity, apparent in shortness of breath when climbing stairs, when walking distances, or with sudden bursts of physical exertion.

The lungs are subject to few BIRTH DEFECTS. Congenital disorders of the lungs include hereditary disorders, such as CYSTIC FIBROSIS, and conditions resulting from prematurity or inadequate development of the lungs before birth, such as chronic lung disease of infancy. Cardiovascular anomalies, notably structural malformations such as transposition of the great arteries (TPA) or hypoplastic left heart syndrome (HLHS), affect the integration of function between the heart and the lungs.

Cigarette smoking, CARDIOVASCULAR DISEASE (CVD), and long-term exposure to irritants such as industrial chemicals are the leading causes of acquired pulmonary disease. Because the lungs face continual exposure to external pathogens, they are vulnerable to viral, bacterial, and fungal invaders. Immune cells—notably lymphocytes, macro-phages, and neutrophils—reside within the walls of the bronchi, detecting and eliminating most pathogens before they can cause localized INFECTION. However, those that slip through the body's defense mechanisms can cause serious diseases such as PNEUMONIA (viral or bacterial).

HEALTH CONDITIONS THAT CAN AFFECT THE STRUCTURES OF THE PULMONARY SYSTEM

ANTHRACOSIS	APNEA
ASBESTOSIS	ASPERGILLOSIS
ASPIRATION	ASTHMA
ATELECTASIS	BERYLLIOSIS
BRONCHIECTASIS	BRONCHITIS
BYSSINOSIS	CHRONIC OBSTRUCTIVE
CYSTIC FIBROSIS	PULMONARY DISEASE (COPD)
LEGIONNAIRES' DISEASE	INTERSTITIAL LUNG DISORDERS
LUNG CANCER	LUNG ABSCESS
Pneumocystis carinii	PLEURISY
PNEUMONITIS	PNEUMONIA
PULMONARY EDEMA	pulmonary congestion
PULMONARY FIBROSIS	PULMONARY EMBOLISM
RESPIRATORY FAILURE	PULMONARY HYPERTENSION
tuberculosis	SILICOSIS

Inefficient cardiovascular function places significant strain on pulmonary function, influencing

the respiratory rate as well as pressuring the network of blood vessels within the lungs to cause conditions such as PULMONARY HYPERTENSION. Congestive HEART FAILURE develops when the heart is not strong enough to pump blood throughout the body, allowing fluids to seep from the bloodstream and into the interstitial spaces in the lungs. The resulting pulmonary congestion and PULMONARY EDEMA fills the lungs with fluid, restricting the oxygen–carbon dioxide exchange. Exposure to environmental irritants and toxins also can damage the lungs, particularly as a cumulative effect over time, causing repeated INFLAMMATION that can result in SCAR formation (fibrosis).

Traditions in Medical History

Ancient Western and Eastern medical traditions alike correlated the function of the lungs with the role of bringing life-giving air, and the NUTRIENTS it bears, into the body. Greek physician Galen (129–199), whose views framed the perceptions and practices of medicine for nearly 1500 years, postulated the lungs took in and digested air, after which the pulmonary VEIN carried the resulting "vapors" to the heart. Though this hypothesis held the correct intent, its details were enough skewed to thwart genuine understanding of cardiopulmonary circulation for centuries.

The concepts of cardiovascular circulation and pulmonary function finally began to converge with William Harvey's detailed monograph, *Exercitatio Anatomica De Motu Cordis et Sanguinis in Animalibus*, published in 1628. This work, whose title translates as *A Treatise on the Movement of the Heart and Blood in Animals*, provided the first definitive description of the circulation of the blood through the heart, lungs, and blood vessels. Harvey failed to identify the capillary beds and their role in oxygen–carbon dioxide exchange; yet his work established the foundation for later researchers to make this and other discoveries about lung function.

Once physicians understood the basic functioning of the lungs, heart, and blood, they could begin to find the causes of the diseases that disrupted these functions, often with debilitating or fatal results. Throughout documented history, TUBERCULOSIS—consumption, as early cultures called this infection that appeared to "consume" its sufferers—has reigned as one of the most devastating diseases known to afflict humankind. The disease causes inflammation, granulation, and calcification within the inner structures of the lungs, permanently destroying lung tissue. Unchecked, tuberculosis spreads within the infected person to fully involve the lungs and often other organs such as the KIDNEYS, spinal fluid, and bones. Early explanations for tuberculosis, which accounted for about 1 in every 20 deaths across centuries and civilizations, ranged from dietary habits such as eating meat and drinking liquor to environmental exposures such as foul weather and smoke from burning fires. In fact, however, tuberculosis spreads among people through contact with bacteria in the SPUTUM (the mucus, fluids, and debris coughed from the lungs) of those who are infected.

Ancient Egyptian mummies demonstrate BONE damage characteristic of tuberculosis. Even famed Western physician of antiquity and Galen's predecessor Hippocrates (460–400 B.C.E.) wrote of the physical wasting that accompanied tuberculosis and warned against close contact, even by physicians, with those in the end stages of the disease. Not for nearly two millennia after him, however, did physicians make the connection between close contact and the contagiousness of tuberculosis. In 1882 microbiologist Robert Koch (1843–1910) discovered the responsible bacillus, *Mycobacterium tuberculosis*, turning the corner toward finding a true cure for the infectious and debilitating disease. Though a cure was still another 60 years away, isolating those who were ill became the trend. Doctors sent those afflicted with tuberculosis to sanatoriums where fresh air, rest, and nutritious meals formed the core of treatment. It was enough for some, though not most, people to recover or at least to send the disease into inactivity—and it separated the infectious from the healthy, helping slow contagion. Some people underwent more dramatic therapies, such as intentional collapse of the infected lung, to try slow the progression of the disease by starving the tissue of oxygen.

In 1943 biochemist Selman Waksman was able to isolate and cultivate an effective antibiotic, streptomycin, to kill *M. tuberculosis* without also killing the person this stubborn PATHOGEN infected. By the early 1960s researchers had developed a regimen of multiple antibiotics to successfully cure

tuberculosis, and over the next 20 years tuberculosis dramatically subsided in developed countries. Tuberculosis resurfaced as a significant health threat with the emergence of HIV/AIDS in the 1990s, however, with new strains of the bacillus that were resistant to previously successful antibiotics. New generations of antibiotics have become available, though *M. tuberculosis* continues to mutate into resistant forms. Today, this destructive infection of the lungs persists.

With the advent of modern industrialization came a surge of induced diseases, many of which exposed the lungs to various particulates such as coal dust (miner's lung), silica (grinder's rot), and plant fibers (mill FEVER). These and other occupational lung diseases have disabled and killed millions of people through the centuries and continue to threaten health even today despite precautions to reduce the risks of exposure.

Miner's lung (ANTHRACOSIS), also called black lung, once disabled nearly every coal miner who worked longer than a few years in the mines and today remains a significant occupational disease threat. SILICOSIS, long a risk for workers in occupations with exposure to sand dust, appears in the lungs of mummies from ancient Egypt, a consequence of the intensely blowing sands of the region, and in the lungs of contemporary workers in quarries, potteries, and industries that use sandblasting. Although new exposures to asbestos are uncommon, the long time from exposure to the development of disease means symptoms arise in people today whose exposure through employment (such as shipbuilding or insulation work) took place decades ago. Though not as common as before modern ventilation and dust control mechanisms became commonplace, long-term inhalation of cotton fibers by textile workers results in BYSSINOSIS—mill fever.

Today lung disease related to industrial practices remains a key component of public health. The use of respirators, exhaust venting, and exposure limitations helps reduce, but does not completely prevent, occupational lung diseases. Some of these conditions are treatable; others are progressive or cause permanent damage. General air pollution resulting from industrial and motor vehicle exhaust accounts for much ASTHMA, chronic BRONCHITIS, PNEUMONITIS, and other ailments of the lungs. ENVIRONMENTAL CIGARETTE SMOKE (secondhand smoke) has further emerged as a dangerous and potentially lethal toxin of exposure. The air that bears life-giving oxygen also transports, sometimes unknowingly, the agents of lung damage.

OCCUPATIONAL LUNG CONDITIONS

ANTHRACOSIS	ASBESTOSIS
ASTHMA	BERYLLIOSIS
BYSSINOSISchronic BRONCHITIS	HYPERSENSITIVITY PNEUMONITIS
INTERSTITIAL LUNG DISORDERS	mesothelioma
PULMONARY FIBROSIS	SILICOSIS

Breakthrough Research and Treatment Advances

The unraveling of the human GENOME has produced significant breakthroughs in understanding and treating health conditions affecting all body systems. Key discoveries related to pulmonary disorders have in particular improved treatment for CYSTIC FIBROSIS, once a disease that claimed the lives of its victims before they reached ADOLESCENCE. Today it is more common than not for those who have cystic fibrosis to enjoy reasonable QUALITY OF LIFE into their early 30s, with new treatments based on GENE THERAPY showing great promise for arresting the progress of this debilitating genetic disorder. LUNG TRANSPLANTATION is emerging as a promising, viable treatment for end-stage pulmonary disease resulting from disorders such as cystic fibrosis, pulmonary hypertension, CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD), and PULMONARY FIBROSIS.

A

acute respiratory distress syndrome (ARDS) A complex of symptoms, formerly called adult respiratory distress syndrome, in which respiratory distress and RESPIRATORY FAILURE develop accompanying severe illness or trauma. ARDS involves the whole of both LUNGS, as the lungs become inflamed and fill with fluid. ARDS may develop as a consequence of injury that directly affects the lungs (notably blunt trauma to the chest, near drowning, PNEUMONIA, and smoke inhalation) or when the injury or illness affects other parts or systems of the body. Systemic INFECTION (SEPSIS), DRUG OVERDOSE, and BLOOD TRANSFUSION may also result in ARDS. ARDS can affect people of any age and is life-threatening. Because people who develop ARDS are already very ill, ARDS has a high death rate (about 40 percent). The syndrome may cause complete respiratory failure or lead to total system failure, either of which presents significant challenge for recovery.

Symptoms and Diagnostic Path

People who develop ARDS have generally sustained severe trauma or infection and most are already in the hospital when their symptoms begin. Early symptoms of ARDS include restlessness, TACHYPNEA (rapid, shallow breathing), and HYPOXIA (reduced oxygen to the body's tissues). ARDS progresses rapidly to full involvement of the lungs. Chest X-rays show the filling of the lungs with INFLAMMATION and fluid (called diffuse infiltration). Arterial BLOOD gases show the decreased percentage of oxygen in the blood. Doctors often perform tests on SPUTUM and fluid from the lungs to identify any pathogens, notably BACTERIA, that may be present.

Treatment Options and Outlook

Immediate oxygen supplementation is essential. Many people require MECHANICAL VENTILATION with positive end expiratory pressure (PEEP) to increase the amount of oxygen entering the lungs. Doctors generally administer sedation while the person is on mechanical ventilation, to provide comfort and to prevent the natural tendency to fight the intervention. Treatment primarily is supportive, including close monitoring of cardiovascular and renal (kidney) functions. Because infection, either in the lungs or elsewhere in the body, is often present, many people may also receive intravenous (IV) ANTIBIOTIC MEDICATIONS.

The outlook for full recovery depends on numerous factors including the person's age, general health status, and the ability to reverse the circumstances responsible for the initial development of ARDS. Even medical intervention that begins early in the course of ARDS cannot predict the success of treatment. About 60 percent of people survive the ARDS episode, though the severity of illness can require extensive recuperation.

Risk Factors and Preventive Measures

The primary risk factors for ARDS are sepsis (severe infection) and major trauma, either to the lungs or to the body in general. Though such infection or trauma alerts doctors to the grave risk for ARDS, there are no known measures that can head off the development of ARDS. Public health measures to minimize the risk factors (trauma and infection) are critical. Once ARDS occurs, however, aggressive medical intervention and support provide the best chance for survival.

See also HEART FAILURE; SEVERE ACUTE RESPIRATORY SYNDROME (SARS).

aging, pulmonary changes that occur with The LUNGS and tracheobronchial structures undergo few but significant changes over the course of the life-

span. From moments after birth to near the end of life the lungs function continuously and consistently, bringing air into the body to deliver oxygen to the BLOOD and carrying air out of the body to eliminate carbon dioxide and other gaseous metabolic wastes from the body. The entire respiratory process—BREATHING and oxygenation—takes place under the regulation of the brainstem, without conscious awareness or control.

Before birth, though the lungs go through the movements of breathing they do not oxygenate the fetus's blood. Rather, the fetus draws its oxygen from the mother's blood through the PLACENTA where oxygen molecules migrate across the capillary membranes from the mother's blood supply to the fetus's blood supply. Differences in the cardiovascular system of the fetus further support this mechanism of oxygenation. In the unborn child the HEART shunts blood from the right atrium to the left atrium through an opening in the atrial septum (wall of muscle that separates the right atrium and the left atrium) called the foramen ovale. Blood also passes from the PULMONARY ARTERIES to the AORTA through an opening called the ductus arteriosus, bypassing the lungs.

The newborn's first breath fills the lungs with air, setting in motion a sequence of events that results in the closure of these openings in the heart and the rerouting of blood flow from the right side of the heart to the lungs and from the lungs to the left side of the heart. As the lungs fully expand after a few breaths, they take over complete responsibility for oxygenating the body. The lung tissue produces a chemical called surfactant, a fluid that coats the inner layer of the lung surfaces to maintain appropriate surface tension to keep the alveoli from collapsing with each exhaled breath, much in the same fashion moisture inside a balloon keeps the walls of the balloon from sticking together when the balloon deflates. These changes may lag in an infant born prematurely, giving rise to breathing and oxygenation difficulties until the lungs can more fully develop.

The lungs continue to function in the same responsibility for the remainder of life, with few changes beyond growing as the body grows. Lung capacity (the ability of the lungs to hold air) and diffusing capacity (the ability of the lungs to transfer oxygen to the blood) peak in the early 20s, after which both slowly but steadily decline until by about age 75 they are roughly half what they were at age 25. Beginning at age 35, lung capacity diminishes about 5 percent every 10 years. In the 50s the muscles of breathing begin to stiffen and lose resilience, though in counterbalance changes within the lungs and airways occur to reduce the resistance air encounters during inhalation. Regular aerobic CONDITIONING throughout life can offset many of the functional implications of these changes, allowing strong pulmonary performance well into the 70s or beyond.

The health conditions affecting the lungs before age 30 tend to be acute (of sudden onset and contained duration), often INFECTION such as viral or bacterial BRONCHITIS, pleuritis, and PNEUMONIA. Chronic (ongoing) health conditions affecting the lungs become increasingly common with advancing age, in part because the natural changes in the lungs may precipitate them and in part because other health situations or environmental factors begin to have cumulative consequences.

CARDIOVASCULAR DISEASE (CVD), which becomes more common in middle age and beyond among both men and women, can have as much effect on the structures and functioning of the pulmonary system as do conditions of the lungs. HEART FAILURE, in which the heart cannot pump enough blood to meet the body's oxygen needs, allows fluid to back up into the lungs. The resulting circumstances, pulmonary congestion and PULMONARY EDEMA, flood the alveoli and prevent them from conducting the OXYGEN–CARBON DIOXIDE EXCHANGE. Chronic HYPERTENSION (high BLOOD PRESSURE) diminishes the elasticity of all arteries in the body, including the pulmonary arteries. The resulting stiffness and inflexibility of the arteries can contribute to or exacerbate cardiovascular conditions such as heart failure. Other forms of cardiovascular disease may result in PULMONARY HYPERTENSION, increased pressure within the pulmonary arteries that damages the smaller arteries within the lungs.

External factors also influence pulmonary health throughout life. Cigarette smoking is the single-most destructive exposure the lungs typically face, causing an extremely high risk for progressive disorders such as CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) and especially for LUNG CANCER. Cigarette smoking accounts for 85 percent

of lung cancer in the United States. Over time breathing exposes the respiratory tract to numerous insults from substances such as environmental pollution, viruses, BACTERIA, pollens, dust, and other materials. These exposures may injure or damage the lungs, resulting in conditions such as ASTHMA, PNEUMONITIS, bronchitis, and pneumonia, as well as infections such as TUBERCULOSIS and INFLUENZA. Such pulmonary conditions can contribute to deteriorating lung functions, particularly in people who have not maintained adequate AEROBIC FITNESS.

Maintaining a steady level of AEROBIC FITNESS through regular physical activity keeps the pulmonary system as healthy as possible for as long as possible, helping offset the changes of advancing age. Aerobic fitness enables the lungs to efficiently extract oxygen from the air and conduct it into the bloodstream. As well, the lungs fill more fully with air on each inhalation, keeping the alveoli open and functioning. This helps keep fluid from accumulating within the alveoli.

See also AGING, CARDIOVASCULAR CHANGES THAT OCCUR WITH; AGING, CHANGES IN THE BLOOD AND LYMPH THAT OCCUR WITH; ASPIRATION; CONGENITAL HEART DISEASE; PLEURISY; SMOKING AND HEALTH.

alveolus A tiny, thin-walled sac, grouped in clusters at the ends of the smallest airways (bronchioles) deep inside the LUNGS, that is the terminus for each breath of air. A dense mesh of capillaries entwines each alveolus. Oxygen from the air within the alveolus passes across the alveolar membrane to enter the bloodstream, while carbon dioxide and other waste gases pass across the membrane from the BLOOD to the air within alveolus. The clustered formations of the alveoli greatly increase the surface area for OXYGEN–CARBON DIOXIDE EXCHANGE. Each lung contains about 300 million alveoli, which, if spread out, would coat the surface of a tennis court—about 290 square feet. The large surface area is important but so is the very thin interface between the airway and the blood vessel. Many disease states cause this barrier to thicken or distort, which impedes the exchange of oxygen and carbon dioxide (called decreased diffusing capacity).

For further discussion of the alveolus within the context of pulmonary structure and function please see the overview section "The Pulmonary System."

See also BRONCHUS; HEMOGLOBIN; TRACHEA.

anthracosis A lung condition resulting from long-term exposure to coal dust, also called coal worker's PNEUMONOCONIOSIS (CWP) and black lung disease. There are two types of anthracosis: simple and complicated. In simple anthracosis the coal dust coats the LUNGS in wide distribution, and the IMMUNE RESPONSE encapsulates the dust particles without causing scarring (fibrosis). This is the most common type of anthracosis and may generate no symptoms or mild symptoms such as DYSPNEA (shortness of breath) with exertion and chronic COUGH. The doctor may detect simple anthracosis during routine medical examination or screening for lung disease. Diagnosis generally considers X-RAY findings in combination with history of exposure to coal dust. The doctor may also conduct BRONCHOSCOPY to examine the inner bronchial structures, which have a characteristic black appearance.

Complicated anthracosis becomes aggressively fibrotic, though doctors do not know what causes it to do so. It continues to progress even after exposure ends, and may result in disabling obstructive lung disease. Symptoms include worsening cough and dyspnea. About 15 percent of coal workers who have simple anthracosis develop complicated anthracosis.

Improvements in mining techniques and conditions, including environmental filtration systems, have greatly reduced the amount of dust coal mining operations produce. Those who work as cutters, loaders, and continuous mining operators face the highest risk for exposure. In the United States, the Occupational Safety and Health Administration (OSHA) regulates permissible levels of dust and worker exposure. Diagnosis of new cases of anthracosis is steadily declining as a result. Federal health programs provide medical care and other benefits for coal workers who have anthracosis.

See also ASBESTOSIS; BERYLLIOSIS; BYSSINOSIS; CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD); SILICOSIS.

apnea The temporary and involuntary cessation of BREATHING. Apnea may result from neurologic

causes (central apnea), mechanical causes (obstructive apnea), or a combination of both. Central apnea is more common in premature infants, whose nervous systems are not fully developed, and the very elderly, whose nervous systems may be failing. Central apnea is also more common in people who have underlying neurologic disorders or who have heart failure. Obstructive apnea may occur in children who have greatly enlarged tonsils or adenoids and in individuals who have OBESITY. Some people have irregular breathing patterns that are, for them, normal. A doctor should evaluate irregularities in breathing to determine whether the circumstances merit medical intervention.

Most people who have apnea are unaware of apneic episodes, though others who observe them may become alarmed (especially parents or caregivers who notice apnea in young children). Recurrent apnea that occurs during sleep, called OBSTRUCTIVE SLEEP APNEA, is a serious health condition that disrupts the sleeping patterns and results in sleep deprivation though most people are not aware of this because they do not have conscious recollection of the apneic episodes. Researchers believe that severe and persistent obstructive sleep apnea contributes to cardiovascular conditions such as HEART FAILURE.

The diagnostic path includes careful analysis of apnea patterns, taking into consideration the person's age, the onset of the apnea, and adverse effects that may result (including effects resulting from sleep deprivation). The pulmonologist may conduct pulmonary function tests, BLOOD tests to measure levels of erythrocytes (red blood cells) and HEMOGLOBIN in the blood, and X-rays or other diagnostic imaging procedures to look for obstructive causes. A comprehensive NEUROLOGIC EXAMINATION, including ELECTROENCEPHALOGRAM (EEG), may reveal the cause of central apnea.

Treatment targets the underlying cause of the apnea. For some people, surgery to remedy the cause of an obstruction may provide long-term relief (such as TONSILLECTOMY and ADENOIDECTOMY in children who have enlarged tonsils and adenoids). Central apnea that results from damage to the brainstem or other underlying neurologic disorder can be difficult to treat. Oxygen therapy alone may help with some central apneas.

See also ASPHYXIA; CHEYNE-STOKES RESPIRATION; DYSPNEA; SUDDEN INFANT DEATH SYNDROME (SIDS); TACHYPNEA.

asbestosis Damage to the LUNGS resulting from inhalation of asbestos fibers. During the first half of the 20th century asbestos, a natural substance mined from underground, became common in insulating materials because of its natural heat resistance. In the 1950s researchers linked chronic asbestos inhalation with PULMONARY FIBROSIS and a rare form of LUNG CANCER, mesothelioma, found almost exclusively in people with asbestos exposure. In the 1970s the United States implemented strict regulations that prohibited the use of asbestos in many of its formerly common applications. For people who had occupational exposure to asbestos before these restrictions, however, asbestosis is a significant risk. Millions of Americans live with asbestosis and hundreds die each year from it or from lung cancer associated with asbestos exposure.

Asbestos fibers embed in the tissues of the lungs, causing INFLAMMATION and granulation that eventually leads to fibrosis (SCAR tissue formation). Some forms of asbestos are more hazardous than others. Typically lung damage from asbestos takes 20 years or longer after exposure to manifest. The likelihood of developing health consequences from asbestos exposure correlates directly to the amount of asbestos and the duration of the exposure. Cigarette smokers face increased risk, particularly of lung cancer, as the asbestos and the carcinogenic chemicals in cigarette smoke potentiate each other (intensify each other's actions in the lungs).

Symptoms and Diagnostic Path

Many people do not show symptoms of asbestosis until the damage is fairly advanced. Because of this, health experts recommend people with known asbestos exposure receive annual examinations to monitor the health of their lungs. When symptoms manifest they typically include

- DYSPNEA (difficulty BREATHING) with physical exertion
- dry (nonproductive) COUGH
- chest discomfort, tightness, or PAIN

The diagnostic path includes comprehensive work and health histories, physical examination including AUSCULTATION, chest X-rays, and sometimes other diagnostic imaging procedures such as COMPUTED TOMOGRAPHY (CT) SCAN or MAGNETIC RESONANCE IMAGING (MRI). Finger clubbing, in which the ends of the fingers become thick, rales (crackling BREATH SOUNDS), and CYANOSIS (bluish hue to the lips and SKIN that signals inadequate oxygenation) are common signs of lung damage typical of lung diseases such as asbestosis. Doctors assign a numeric classification from grade 0 to grade 4 to indicate the severity of damage, along with letter designations A, B, or C to identify the extent of lung structure affected.

Treatment Options and Outlook

Treatment for asbestosis is largely supportive, as it is not possible to remove the fibers once they embed in the lungs. SMOKING CESSATION is of prime importance, as cigarette smoking in combination with asbestos exposure greatly increases the likelihood of lung cancer. Treatment also targets specific concerns or other problems as they arise. Generalized efforts to promote pulmonary health, such as BREATHING EXERCISES and regular physical activity to improve AEROBIC CAPACITY, increase the efficiency of undamaged lung tissue.

Because the latency period (time between exposure and symptoms) is so long, damage to the lungs can be quite extensive by the time symptoms become apparent. People who know they have had exposure to asbestos should have regular pulmonary examinations to monitor for asbestosis. Though asbestosis can be fatal, many people live without significant complications due to the condition. The most significant consequence of asbestosis is lung cancer, including mesothelioma, a type of lung cancer that only occurs with asbestos exposure.

Risk Factors and Preventive Measures

Asbestosis only occurs as a consequence of asbestos exposure, so eliminating exposure eliminates the risk of developing the condition. Preventive measures for those who continue to have occupational exposure include appropriate protective clothing and respirators.

See also ANTHRACOSIS; BERYLLIOSIS; BYSSINOSIS; LIVING WITH CHRONIC PULMONARY CONDITIONS; SILICOSIS; SMOKING AND PULMONARY DISEASE.

aspergillosis An opportunistic fungal (yeast) INFECTION that can manifest as PNEUMONIA in people who have HIV/AIDS, are undergoing CHEMOTHERAPY to treat cancer, receive IMMUNOSUPPRESSIVE THERAPY

ASBESTOSIS SEVERITY

Grade	Severity	Extent of Lung Damage
grade 0	asymptomatic	asbestos fibers present but no fibrosis
grade 1	mild damage	fibrosis limited to bronchi and bronchioles, no alveolar involvement
grade 2	moderate damage	fibrosis extends to alveoli
grade 3	serious damage	fibrosis extends between alveolar clusters
grade 4	severe damage	fibrosis obliterates alveoli, replacing them with honeycombed SCAR tissue
grade a	mild involvement	scattered bronchial structures are involved
grade B	moderate involvement	fewer than half the bronchial structures are involved
grade C	severe involvement	greater than half the bronchial structures are involved

after ORGAN TRANSPLANTATION, or are otherwise IMMUNOCOMPROMISED. Aspergillosis may also occur as an allergic reaction (called allergic bronchopulmonary aspergillosis or ABPA) in people who have ASTHMA or CYSTIC FIBROSIS, causing airway INFLAMMATION and fluid accumulation in the LUNGS. *Aspergillus*, the infective FUNGUS, is common in the environment, especially in decaying vegetation and in the soil, and in air ventilation ducts in buildings. Hospitals also harbor *Aspergillus*, so aspergillosis can develop as a nosocomial infection. Occasionally aspergillosis takes the form of an encapsulated ball, called an aspergilloma or a mycetoma, that forms within a pocket of healed SCAR tissue from previous damage to the lung such as may remain from TUBERCULOSIS or SARCOIDOSIS.

Symptoms and Diagnostic Path

Symptoms of aspergillosis vary widely and may not appear at all unless the fungus establishes itself within the lungs in a widespread pattern. When symptoms are present they typically include

- HEMOPTYSIS (bleeding from the lungs that appears in the SPUTUM or coughing up BLOOD)
- CHEST PAIN
- FEVER
- COUGH
- rapid or difficult BREATHING (DYSPNEA)

The doctor also may suspect aspergillosis in a person who has been receiving treatment for an apparent bacterial infection without any improvement in symptoms. The diagnostic path typically begins with a chest X-RAY, which shows whether there are infiltrates or obstructions in the lungs. COMPUTED TOMOGRAPHY (CT) SCAN often can provide more detailed visualization of lung structures and anomalies. Though imaging results are not conclusive, they provide leading clues to suggest or rule out aspergillosis. Because aspergillosis spores are so common in the environment, sputum cultures are not usually helpful in making the diagnosis as nearly everyone's sputum is likely to contain some *Aspergillus*. BRONCHOALVEOLAR LAVAGE, in which the pulmonologist rinses cell samples from the walls of the bronchi during BRONCHOSCOPY, or biopsy to obtain tissue samples, may provide more accurate culture results. The individual's health history also plays a key role in making the diagnosis.

Treatment Options and Outlook

Invasive aspergillosis is life-threatening and requires treatment with intravenous (IV) ANTIFUNGAL MEDICATIONS such as amphotericin B, itraconazole, or voriconazole. Recovery depends on the IMMUNE SYSTEM's ability to rally against the infection. In people who are immunocompromised, the challenge may be overwhelming. In such situations aspergillosis can have serious and even fatal consequences. However, most people fully recover with appropriate treatment. Aspergillomas may require surgery to remove them when they cause bleeding (evident as hemoptysis), pain, or difficulty breathing. CORTICOSTEROID MEDICATIONS such as prednisone are usually effective in relieving the symptoms of ABPA, which is an immune reaction to the presence of *Aspergillus,* common in people who have asthma, rather than an invasive infection with the fungus.

Risk Factors and Preventive Measures

People who are taking immunosuppressive therapy, such as after organ transplantation, or who are immunocompromised are vulnerable to invasive aspergillosis because their immune systems cannot fend off this ordinarily innocuous fungus. Aspergillosis is also a risk for people who have HIV/AIDS. Though there are no measures for preventing aspergillosis, those who are susceptible to this fungal infection can minimize the severity of disease by seeking medical diagnosis and treatment at the earliest indication of disease.

See also BRONCHIECTASIS; NEUTROPENIA.

asphyxia The inability of the LUNGS to take in air or conduct the OXYGEN–CARBON DIOXIDE EXCHANGE, depriving the body of oxygen.

Asphyxia is a life-threatening emergency that requires immediate medical treatment.

Asphyxia may occur as a consequence of water or other fluids in the lungs (drowning) that results in suffocation (inability of air to enter the lungs), carbon monoxide poisoning, trauma to the TRA-

CHEA (windpipe), injury to the brainstem affecting the NERVOUS SYSTEM signals that regulate breathing, compression of the neck or chest, electrical shock, cardiovascular collapse, and other circumstances that interfere with BREATHING. A person experiencing asphyxia may require immediate CARDIOPULMONARY RESUSCITATION (CPR) until medical care is available.

See also HYPOXIA.

aspiration Drawing foreign matter, often food or drink, into the airways (TRACHEA and bronchi). The COUGH REFLEX typically activates to expel the matter, though may not succeed if inhalation draws the matter deep into the respiratory tract or the cough reflex is weak. Food, drink, and other substances that coughing does not expel can lodge in the airway to create a partial or complete obstruction.

Aspiration is potentially life-threatening and may require emergency intervention such as the HEIMLICH MANEUVER. A doctor should evaluate the condition of the LUNGS when aspiration occurs.

Material that makes its way deep into the LUNGS is likely to draw BACTERIA and fluid to the site, establishing inflammation, edema, PNEUMONIA, or LUNG ABSCESS. Physical movement such as sitting, standing, and walking may help the respiratory tract propel the substance outward, while inactivity allows the matter to settle into the lungs. Near drowning often results in aspiration of water into the lungs.

A chest X-RAY typically shows the site of INFLAMMATION and fluid collection. Treatment may require BRONCHOSCOPY to retrieve the object and ANTIBIOTIC MEDICATIONS to treat INFECTION. Aspiration pneumonia is a potentially serious condition, particularly in the elderly, infants, and debilitated people who cannot easily move around or who may have trouble with the natural mechanisms that protect the airway, resulting in foreign matter getting into the lungs. Aspiration pneumonia develops when the accumulated fluid becomes infected or interferes with the ability of the lungs to oxygenate the BLOOD.

See also BRONCHUS.

asthma A disease of the airways that results in narrowing of the airways (bronchospasm) and INFLAMMATION in response to a wide range of inhaled irritants such as pollen, mold, smoke, chemicals, and the airborne debris of pests ranging from cockroaches to microscopic dust mites. This narrowing, or airflow obstruction, is usually reversible when the person can eliminate the exposure or through treatment with medications called bronchodilators. Repeated exposure to irritants in susceptible people can result in repeated episodes of inflammation. This pattern can ultimately cause scarring of the airways that is not reversible.

Nearly 18 million Americans have asthma, a third of whom are under age 18. For many of them asthma attacks are mild and infrequent, giving the perception that asthma is a common and, though annoying, harmless condition. However, life-threatening consequences can occur during a severe asthma attack. If the person does not receive rapid and effective treatment, the airway narrowing and inflammation can completely block the flow of air. The person cannot exhale (breathe out) fully, lowering oxygen levels and potentially causing death. Nearly 5,000 Americans die each year as a consequence of asthma or its complications.

Symptoms and Diagnostic Path

An asthma attack generally follows a pattern of symptoms that, though it varies among people who have asthma, tends to be consistent for each individual. Some people first experience DYSPNEA (shortness of breath) or wheezing (a high-pitched whistling sound with exhalation), for example, while other people find a restless night with frequent waking foreshadows an asthma attack that manifests the following day. Common symptoms of asthma attacks include

- dry, nonproductive COUGH
- sense of tightness in the chest
- dyspnea, especially during physical activity
- wheezing
- gasping for air

There are no definitive tests for asthma. The diagnostic path may include tests and procedures,

such as chest X-RAY and complete BLOOD count (CBC), to rule out other causes of symptoms. The pulmonologist will conduct pulmonary function tests to measure the flow and volume of air, typically before and after administration of a bronchodilator medication that relaxes and opens the airways. People who have asthma generally have much improved pulmonary function test results after the bronchodilator, even when they are having no symptoms of asthma at the time of testing. However, the reverse can also be true and the person has normal breathing tests during a time of no symptoms. In such cases, the pulmonologist may conduct a test called a methacholine challenge, administering the DRUG methacholine to see whether it initiates a mild hypersensitivity reaction. A positive response (symptoms appear) is fairly conclusive of an asthma diagnosis.

Treatment Options and Outlook

Treatment for many people who have asthma is a combination of medications to prevent symptoms (long-acting, controller medications) and to provide immediate relief from symptoms that occur (short-acting, rescue medications). Medication regimens vary with the step (classification) and nature of symptoms. Commonly prescribed medications include

- inhaled (and occasionally oral) CORTICOSTEROID MEDICATIONS, which are anti-inflammatory and serve as long-term controller medications
- inhaled and oral beta-2 agonists, which are bronchodilators and may provide short-acting or long-acting relief
- leukotriene modifiers, which are IMMUNE RESPONSE mediators that provide long-term control

The mainstay of asthma treatment is baseline control of the inflammation with long-acting medications. For some people, ALLERGY DESENSITIZATION (when allergy reaction is the clear cause of the asthma) provides further control. Other important steps for managing asthma long-term include monitoring asthma symptoms (such as with peak flow monitoring) and developing an action plan for asthma control. When there is an acute exacerbation of symptoms (an asthma attack), treatment is most likely to succeed when it begins in advance of or immediately on recognition of symptoms. Once an asthma attack is under way, even rescue medications may take time to bring the situation under control.

Lifestyle factors for managing asthma include avoiding known triggers and allergens. Three of the most common triggers are allergic RHINITIS, chronic SINUSITIS, and GASTROESOPHAGEAL REFLUX DISORDER (GERD). Regular physical exercise, though for some people a trigger for asthma attacks, generally improves lung capacity, pulmonary efficiency, and AEROBIC FITNESS. Air-conditioning helps reduce humidity in the air and filter the air of particulates that may cause irritation or exacerbate asthma symptoms. It is important to regularly change the air filters for central heating and cooling systems. ACUPUNCTURE treatments are helpful for reducing the frequency and severity of asthma attacks in some people.

ASTHMA CLASSIFICATION

Classification	Severity	Frequency of Symptoms Without Treatment
step 1	mild intermittent	symptoms occur two days or less each week and two nights or less each month
step 2	mild persistent	symptoms occur up to five days each week and up to five nights in a month
step 3	moderate persistent	symptoms occur at least once during every day and several nights a week
step 4	severe persistent	symptoms occur throughout the day, every day, and most nights

MEDICATIONS TO TREAT ASTHMA

Type of Medication	Common Products	Type of Relief	Asthma Classification
beta-2 agonists, inhaled	albuterol (Airet, Proventil, Ventolin), bitolterol (Tornalate), pirbuterol (Maxair)	short-acting rescue	steps 1, 2, 3, or 4
beta-2 agonists, oral	long-acting: salmeterol (Serevent), albuterol extended release (Volmax, Proventil Repetabs) short-acting: terbutaline (Brethine, Bricanyl)	long-acting: controller medication, especially at night short-acting: rescue	steps 2, 3, and 4
corticosteroids, inhaled	beclomethasone (Qvar, Vanceril), budesonide (Pulmicort), flunisolide (AeroBid), fluticasone (Flovent), triamcinolone (Azmacort)	long-acting controller medication	steps 2, 3, and 4
corticosteroids, oral	methylprednisolone (Medrol), prednisone (Deltasone, Orasone), prednisolone (Prelone)	short-acting controller medication for symptoms that do not respond to other medications rescue	steps 3 and 4
leukotriene modifiers, oral	zafirlukast (Accolate), zileuton (Zyflo)	long-acting controller medication	steps 3 and 4, occasionally step 2
other, inhaled	ipratropium (Atrovent), cromolyn (Intal), nedocromil (Tilade)	short-acting rescue prophylactic when used before intense physical exercise	steps 3 and 4
other, oral	theophylline (Theo-Dur, Theolair, Aerolate, Slo-Phyllin)	long-acting	step 3, occasionally step 2

Risk Factors and Preventive Measures

The key risk factor for asthma attack is exposure to a substance that initiates a hypersensitivity reaction. Most people can easily identify these substances after experiencing a few asthma attacks, and avoiding exposure to known allergens significantly reduces attacks. A wide range of irritants can cause asthma attacks in many people, however, making it impossible to avoid exposure. As well, for some people triggers for asthma attacks include emotional stress and physical exertion, common elements of everyday life.

Health experts have identified a number of factors that appear to increase an individual's risk for developing asthma. Key among them are

- living in cities, where the concentration of particulate pollutants in the air is high
- family history of asthma
- recurrent upper respiratory INFECTION as a child
- cigarette smoking or exposure to ENVIRONMENTAL CIGARETTE SMOKE

- long-term or repeated exposure to chemicals such as cleaning solutions, paints, industrial chemicals used in manufacturing, pesticides and herbicides, and aerosols
- presence of ALLERGIC RHINITIS, atopic DERMATITIS, or chronic SINUSITIS

Viral infections, physical exertion such as with exercise, cold air, sulfite preservatives (common in some foods), some medications, and GASTROESOPHAGEAL REFLUX DISORDER (GERD) also may trigger asthma attacks. Researchers do not know why some people develop hypersensitivity reactions to certain substances while other people, even though their immune systems similarly create antibodies, experience normal reactions. Though researchers believe there are likely genetic factors that underlie allergies, they have yet to isolate them.

See also ALLERGIC ASTHMA; ANTIBODY; ATOPY; BREATH SOUNDS; HYPERSENSITIVITY REACTION; LIVING WITH CHRONIC PULMONARY CONDITIONS; MULTIPLE CHEMICAL SENSITIVITY SYNDROME.

atelectasis The collapse of a segment or lobe of the lung, or an entire lung. Atelectasis is fairly common and most often spontaneously corrects itself for full recovery. The collapse may result from obstruction, structural damage to lung tissue, fibrosis that destroys bronchial segments, PNEUMOTHORAX, PLEURAL EFFUSION, and other causes. A form of chronic atelectasis, right middle lobe syndrome, results from chronic INFLAMMATION of the LYMPH nodes near the area, which are beneath the right lung's middle lobe. A common cause of atelectasis is taking shallow breaths, which is common in people coming out of ANESTHESIA but still sedated after surgery or who have abdominal or chest wall pain.

Symptoms and Diagnostic Path

Symptoms of atelectasis vary with the rate of onset and the extent of lung area involved. Rapid collapse may cause sharp PAIN and sudden DYSPNEA and may also cause severe COUGH. Chronic atelectasis or atelectasis that develops gradually may produce few symptoms, though many people develop a persistent, nonproductive cough.

The diagnostic path begins with careful AUSCULTATION for BREATH SOUNDS. Typically the collapsed segment causes displacement within the thoracic cavity of the affected lung, and often the unaffected lung as well as the HEART. Breath sounds may be normal though heard in abnormal locations. The doctor may also hear wheezes or rales, abnormal breath sounds that suggest blocked airways. Chest X-RAY clearly shows the displacement and the extent of the collapse. In the simplest case, coughing and deep breathing may resolve the atelectasis. In other cases, the doctor may desire additional diagnostic imaging such as COMPUTED TOMOGRAPHY (CT) SCAN to precisely identify the site of the atelectasis as well as the possible cause (such as a tumor or an obstruction). BRONCHOSCOPY may allow the pulmonologist to directly visualize the collapsed area and remove an obstruction such as a foreign object or mucus plug, if that is the cause of the collapse. Bronchoscopy also permits BRONCHOALVEOLAR LAVAGE or biopsy, if indicated.

Treatment Options and Outlook

Often, segmental atelectasis requires no treatment beyond watchful waiting or encouraging deep breathing. The lung will correct itself. Infection requires treatment with ANTIBIOTIC MEDICATIONS; inflammation may require treatment with CORTICOSTEROID MEDICATIONS. Other medications that sometimes relieve discomfort and help the lung restore itself include bronchodilators, which relax and open the airways. CHEST PERCUSSION AND POSTURAL DRAINAGE help keep the lungs free from accumulated secretions, and the doctor may recommend the person lie on his or her unaffected side to allow gravity to help restore the collapsed segment. Rarely, the doctor may consider surgery for chronic atelectasis that fails to respond to medical treatment. Most people recover from atelectasis without complications.

Risk Factors and Preventive Measures

Risk factors for atelectasis include obstructive pulmonary conditions such as CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD), CYSTIC FIBROSIS, chronic BRONCHITIS, and BRONCHIECTASIS. Recent surgery with general anesthesia is a common cause of atelectasis. Though avoiding these circumstances

may not be possible, being alert to the possibility of atelectasis allows medical evaluation and intervention before complications such as infection or PNEUMONIA establish themselves.

See also CYSTIC FIBROSIS AND THE LUNGS; LUNG CANCER; SMOKING AND PULMONARY DISEASE; SURGERY BENEFIT AND RISK ASSESSMENT.

auscultation The diagnostic procedure of listening to the LUNGS using a STETHOSCOPE held to various placements on the chest and back. Auscultation allows the doctor to hear normal and abnormal BREATH SOUNDS, the noises of air flowing through the respiratory tract. The doctor typically listens to the same location for each lung, to compare the sounds, and moves in a side-to-side pattern first across the chest from the apex to base (top to bottom) of each lung and then a similar pattern on the back. When conducting a pulmonary examination, the doctor also listens with the stethoscope placed over the TRACHEA at the throat.

There are four normal breath sounds—tracheal, vesicular, bronchial, and bronchovesicular—all heard upon both inhalation and exhalation. Deviations in tone, loudness, frequency, and character of the sounds help the doctor assess the performance of the lungs. Extra sounds, such as rales and wheezes, are abnormal and signal pulmonary ailments such as BRONCHITIS, ASTHMA, and PNEUMONIA. The doctor usually listens to the HEART as well during auscultation, as the HEART SOUNDS provide additional diagnostic information. The doctor uses the diaphragm of the stethoscope to auscultate for breath sounds and the bell of the stethoscope to auscultate for heart sounds.

See also APNEA; BREATHING; DYSPNEA; TACHYPNEA.

B

berylliosis Chronic damage to the LUNGS, also called chronic beryllium disease, resulting from industrial exposure to beryllium, a heavy metal that has many commercial uses and applications in contemporary manufacturing processes. Inhaled beryllium fumes and dust cause irritation to the delicate alveoli that activates the body's IMMUNE RESPONSE. In the United States berylliosis occurs primarily in people who work in the electronics, nuclear, and aerospace industries where beryllium usage is high. People who work in metal machining or alloy reclamation jobs are also at risk. The US Environmental Protection Agency (EPA) classifies beryllium dust and fumes as toxic substances, and the US Occupational Safety and Health Administration (OSHA) has established regulatory guidelines to minimize on-the-job beryllium exposure. Beryllium particles can remain in the lung tissues for six months to several years after exposure.

Berylliosis results from delayed-type hypersensitivity (DTH) in which helper T-cell lymphocytes flood the sites of exposure and encase the beryllium dust particles or the areas of INFLAMMATION, causing granulomas to form. Over time the granulomas evolve into fibromas, well-defined structures of SCAR tissue that replace normal lung tissue. As the penetration of granulomas and fibromas extends deeper into the lungs, the loss of alveolar function cripples the ability of the lungs to pass oxygen to the BLOOD.

Rarely, an individual may develop an immediate response, called acute chemical PNEUMONITIS, to beryllium exposure. Acute chemical pneumonitis requires prompt medical treatment to reduce airway irritation and INFLAMMATION.

Symptoms and Diagnostic Path

Symptoms of berylliosis are similar to symptoms of other chronic inflammatory diseases affecting the lungs, though employment in an occupation involving beryllium use is a key indication of the cause and nature of disease. Symptoms typically include

- chronic, nonproductive (dry) COUGH
- chest tightness or PAIN
- unintended weight loss
- shortness of breath (DYSPNEA), particularly with exertion
- fatigue

The diagnostic path includes chest X-RAY, BRONCHOALVEOLAR LAVAGE, and a specialized test called the beryllium lymphocyte proliferation test (BeLPT). The pulmonologist may also choose to perform high-resolution COMPUTED TOMOGRAPHY (CT) SCAN, which reveals small lesions within the lungs, and bronchial biopsy via BRONCHOSCOPY to further evaluate lesions that imaging procedures show. Pulmonary function tests and sometimes cardiopulmonary exercise testing can help assess the status of lung capacity and the ability of the lungs to oxygenate the blood. Conclusive diagnosis may require varied and numerous tests as well as thorough medical and personal histories, as berylliosis is similar to other interstitial lung diseases including sarcoidosis.

Treatment Options and Outlook

The first line of treatment is removal from the source of beryllium, which for most people means leaving the jobs that require exposure to beryllium. CORTICOSTEROID MEDICATIONS may help suppress the immune response and subdue the

inflammation. However, there is no known medical therapy to treat damage that has occurred to the lungs. Damage that does occur to the lungs is permanent and berylliosis is usually progressive, tending to continue even after exposure to beryllium ends. The resulting damage to the lungs may lead to HEART FAILURE and other cardiovascular health conditions because the HEART cannot pump enough BLOOD to oxygenate the body's tissues. LUNG TRANSPLANTATION may become a viable treatment option for people who develop complete pulmonary failure.

Risk Factors and Preventive Measures

Recent research suggests GENETIC PREDISPOSITION underlies most cases of berylliosis, with mutations or defects affecting the MAJOR HISTOCOMPATABILITY COMPLEX (MHC), which encodes aspects of immune response. The role of genetic predisposition is not entirely clear, though likely explains why some people who have limited exposure develop serious disease whereas others who have prolonged exposure seem to experience no adverse effects. However, berylliosis occurs only in people exposed to beryllium and nearly all such exposure is occupational, though beryllium is a natural mineral present in the environment. Reducing this exposure through appropriate occupational hygiene and protective measures can significantly reduce the risk of disease development.

MANUFACTURING JOBS WITH HIGH RISK FOR BERYLLIOSIS

aerospace alloys	computer electronics
dental alloys (bridges and crowns)	electrode welding
electronic resistors	heat sinks
jet brake pads	jet turbine blades
laser tubes	metal alloy bicycle frames
metal working	nuclear weapons
semiconductor chips	transistors
X-RAY windows	

People who work in industries in which beryllium use is common should be alert to the early symptoms of berylliosis. Contact with or use of products containing beryllium after their production or manufacture does not convey beryllium exposure, however. Screening blood BeLPT tests among people who work with beryllium can identify early indications of immune reactivity, allowing medical intervention to avert extensive damage to the lungs. OSHA recommends the use of powered respirators with high-efficiency particulate air (HEPA) filters and protective clothing in the workplace, as well as safeguards, such as showering and changing into complete street clothes (including shoes) before leaving the workplace.

See also ASBESTOSIS; BYSSINOSIS; ENVIRONMENTAL HAZARD EXPOSURE; HEAVY-METAL POISONING; OCCUPATIONAL HEALTH AND SAFETY; SARCOIDOSIS.

black lung See ANTHRACOSIS.

breathing The process of drawing air into and expelling air from the LUNGS, also called pulmonary respiration. Specialized centers in the brainstem regulate the rate and rhythm of respiration to harmonize breathing with HEART RATE and BLOOD PRESSURE. Breathing occurs through the mechanical actions of MUSCLE movement. The DIAPHRAGM (the large, flat muscle that extends across the floor of the thoracic cavity) and the intercostal muscles (the muscles between the ribs) contract to expand the thoracic cavity, pulling air into the lungs (inhalation). Inhalation is an active process.

Simultaneously the EPIGLOTTIS, a cartilaginous flap at the top of the throat normally closed across the top of the TRACHEA to prevent food and other materials from entering the lungs, opens to allow the air to pass. The air flows through the trachea into the bronchi, bronchioles, and alveoli. When the diaphragm and the intercostal muscles relax the thoracic cavity returns to its resting position, pressuring air out of the lungs (exhalation) in reverse sequence. Exhalation is a passive process.

Breathing patterns help the doctor assess pulmonary function and respiratory effectiveness. Breathing may be varying combinations of rapid (TACHYPNEA) or slow (bradypnea), regular or irregular, deep or shallow. Though an individual may influence breathing through conscious focus, breathing is an involuntary process under control of the brainstem. The concentration of carbon dioxide in the BLOOD is the primary trigger for initiation of a RESPIRATORY CYCLE (one inhalation and one exhalation), triggering the brainstem to signal the diaphragm and the intercostal muscles to contract.

See also BREATH SOUNDS; HYPERVENTILATION; RESPIRATION RATE.

breathing exercises Methods to improve lung capacity. Breathing exercises are especially helpful for people who have chronic or progressive lung conditions such as CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD), BRONCHIECTASIS, and PULMONARY FIBROSIS. The pulmonologist or respiratory therapist may prescribe specific breathing exercises to accommodate an individual's unique needs and health status. General breathing exercises often recommended include

- belly breathing, which uses the abdominal muscles to help completely fill and empty the LUNGS
- pursed lip breathing, which releases air through lips formed as though to whistle and maintains positive pressure in the airways with exhalation (especially helpful for people who have COPD and other obstructive diseases)
- measured breathing, in which the person breathes in, holds the breath, and breathes out for an equal count at each stage

YOGA breathing is also beneficial for pulmonary health, with yoga breathing exercises to practice in combination with yoga positions as well as simply as breathing exercises. In yoga, the breath is *prana*, the energy of life, and breathing exercises are *pranayama*. Common *pranayama* include

- bellows breathing, in which inhalation is steady and full, with exhalation forceful and rapid
- alternate nostril breathing, in which inhalation is steady and full through one nostril with the fingers holding the other nostril closed, and exhalation through the other nostril, again with the fingers holding the nonbreathing nostril closed
- holding the breath, in which inhalation is steady and full, the lungs hold the breath for as long as is comfortable, and exhalation is steady and slow

For people who have pulmonary health conditions, breathing exercises are more challenging than they sound. It is important to begin slowly and progress steadily. The doctor should approve any planned exercise effort, including breathing exercises. Breathing exercises, including yoga's *pranayama*, are also highly effective for relaxation and stress reduction.

See also AEROBIC EXERCISE; AEROBIC FITNESS; DISABILITY AND EXERCISE; OXYGEN SATURATION; WALKING FOR FITNESS.

breath sounds Characteristic noises the flow of air makes as it courses through the TRACHEA and bronchi. The doctor listens to breath sounds using the diaphragm (flat) side of a STETHOSCOPE placed at various sites on the outside of the chest and the back, a diagnostic method called AUSCULTATION. There are four normal breath sounds, heard with inhalation and exhalation:

- Tracheal breath sounds, hollow sounds heard over the THROAT as air passes through the trachea
- Bronchial breath sounds, harsh sounds heard near the sternum as air passes through the bronchi (large airways in the LUNGS)
- Vesicular breath sounds, rustling sounds heard in most locations on the chest and back as air moves in and out of the alveoli
- Bronchovesicular breath sounds, a mix of harsh and rustling sounds heard just to the sides of the upper sternum on the chest and below the shoulder blades on the back

Normal breath sounds are of nearly equal duration with inhalation and exhalation and are particular to specific locations. Normal breath sounds heard elsewhere are abnormal and indicate the possibility of pulmonary conditions such as ATELECTASIS (collapsed segment of lung), fibrosis (SCAR tissue in the lungs), or other circumstances that cause the lung to shift its physical or functional presence within the thoracic cavity. The absence of normal breath sounds indicates that the segment or lobe of the lung is not receiving air, usually as a result of a significant bronchial occlusion (blockage of a bronchus), severe atelectasis, or lung collapse.

Other breath sounds the doctor can hear through the stethoscope are abnormal and indicate INFECTION or disease. Doctors call these adventitious breath sounds. Among them are

- wheezes, steady high-pitched whistling noise heard with exhalation that is typical of obstructed airways such as might result with ASTHMA, inhaled foreign objects, CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD), and chronic BRONCHITIS
- rales (also called crackles), intermittent crackling noises that may sound fine (like crinkling cellophane) or coarse (like pulling apart a hook and loop fastener) often heard with ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS), PULMONARY EDEMA, BRONCHIECTASIS, and INTERSTITIAL LUNG DISORDERS
- rhonchi, low-pitched, continuous whistling noises heard with exhalation that suggest airways blocked with mucus
- stridor, loud wheezing sounds heard with inspiration when there is an obstruction of the trachea

Stridor is a life-threatening emergency that requires immediate medical attention.

- pleural rub, brushing sounds that indicate INFLAMMATION of the PLEURA (membrane covering the outer surfaces of the lungs) such as occurs with PLEURAL EFFUSION or pleural fibrosis

Breath sounds present important diagnostic information that helps the doctor determine the health status of the lungs as well as assess the progress of conditions under treatment.

See also EPIGLOTTITIS; HEART SOUNDS.

bronchiectasis The dilation of a segment of BRONCHUS. Bronchiectasis may involve several bronchial branches and usually occurs deep within the lung, often in a lower lobe. Though bronchiectasis may be congenital (present at birth) or acquired (develop after birth), congenital bronchiectasis is rare and results when only the core structure of the LUNGS develops and existing bronchi dilate in reaction to the pressure of incoming air. Acquired bronchiectasis commonly develops with chronic lung INFLAMMATION such as results from CYSTIC FIBROSIS or repeated INFECTION (typically chronic BRONCHITIS).

Bronchiectasis represents permanent damage to lung tissue, often with accompanying PULMONARY FIBROSIS (scarring), and loss of lung function in the affected areas. Because of the lung's segmented structure nonaffected segments and lobes of the lung continue to function normally, so the extent to which the bronchiectasis affects respiratory performance depends on the number of segments involved. However, bronchiectasis tends to be progressive.

Suspicion of bronchiectasis becomes valid with the existence of pulmonary conditions known to be predisposing, such as cystic fibrosis and chronic bronchitis. Bronchiectasis may follow recurrent PNEUMONIA, ASPIRATION pneumonia, childhood diseases such as PERTUSSIS (whooping COUGH) in children who have not received IMMUNIZATION, and toxic inhalation (such as smoke or chemical inhalation). IMMUNODEFICIENCY disorders that increase the risk for pulmonary infections also raise the likelihood of bronchiectasis. Symptoms typically develop over months to years and commonly include

- persistent, productive cough more intense in the mornings and just before going to bed
- prodigious SPUTUM production
- HEMOPTYSIS (BLOOD in the sputum)
- wheezing (high-pitched, abnormal BREATH SOUNDS with exhalation)

The diagnostic path includes chest X-rays and COMPUTED TOMOGRAPHY (CT) SCAN. The doctor may further desire BRONCHOALVEOLAR LAVAGE or bronchial biopsy (via BRONCHOSCOPY), sputum cultures, and blood tests. Treatment depends on the findings and may include ANTIBIOTIC MEDICATIONS to treat infections or CORTICOSTEROID MEDICATIONS to treat severe inflammation. Bronchodilator medications may help relax and open undamaged bronchi to improve lung capacity. CHEST PERCUSSION AND POSTURAL DRAINAGE help loosen mucus so the normal mechanisms of the respiratory tract can move it out of the lungs. Rarely, surgery to remove a particularly eroded or chronically infected bronchial segment is necessary. Most people are able to manage bronchiectasis with regular medical evaluation and care (including prompt treatment at the earliest indication of infection).

Regular physical activity and avoiding cigarette smoke are crucial to preserve remaining lung function.

See also ATELECTASIS; AUSCULTATION.

bronchitis INFLAMMATION of the bronchi, the airways that branch from the TRACHEA into the LUNGS. Bronchitis may be viral, bacterial, or the result of irritation such as cigarette smoking or exposure to environmental pollutants. It may also occur as an acute condition that comes on suddenly, runs its course, and heals without lasting damage or persistently recur as a chronic condition.

Acute bronchitis Acute infectious bronchitis is especially common during the "cold and flu" season, when it typically follows a viral INFECTION of the upper respiratory tract. Numerous viruses may be responsible, including ADENOVIRUS, coronaviruses, INFLUENZA viruses, and rhinoviruses. Acute viral bronchitis generally runs its course over a period of five to seven days, during which the person feels and appears ill. A residual COUGH may persist for several weeks after the infection subsides.

Acute irritative bronchitis develops in response to inhaled irritants such as fumes, dust, and smoke (cigarette as well as environmental). Symptoms may be difficult to distinguish from those of ASTHMA, particularly in people who do not have a diagnosis of asthma or who have infrequent asthma attacks. The inhaled substance irritates the lining of the bronchi, causing localized inflammation. Most often, the inflammation and resulting bronchitis subsides over the course of a few days.

Chronic bronchitis Repeated exposure to irritants such as cigarette smoke, occupational chemicals, and environmental pollutants may cause persistent or recurrent bronchial inflammation. By far the most common culprit is cigarette smoking or environmental cigarette smoke exposure (second-hand smoking). The hallmark symptom is persistent, productive cough that continues for three months or longer. Over time, chronic bronchitis may evolve into CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) or BRONCHIECTASIS, two conditions in which damage to the bronchi is extensive and permanent. People who have chronic bronchitis are more vulnerable to bacterial infections such as PNEUMONIA, as well as to complications such as ATELECTASIS (collapse of a bronchial segment).

Symptoms and Diagnostic Path

The symptoms of acute bronchitis include FEVER, productive cough, sore THROAT, and chest discomfort or PAIN, especially when taking a deep breath. SPUTUM that is thick, yellowish green, and foul-smelling suggests bacterial infection. Red or brown streaks in the sputum indicate bleeding, which may be from the irritation of coughing or signal a different diagnosis. The diagnostic path includes AUSCULTATION to listen to BREATH SOUNDS, which are typically normal. The doctor may request a chest X-RAY to rule out other causes of the symptoms. The doctor may also collect a sputum sample for culture if there is any suspicion the infection could be bacterial.

The primary symptoms of chronic bronchitis are productive cough and DYSPNEA (shortness of breath). Physical exertion tends to exacerbate both. The diagnostic path begins with auscultation, which may reveal abnormalities of breath sounds depending on whether there is damage to the bronchial structures. Chest x-ray may show areas of inflammation as well as atelectasis or bronchiectasis if either is present. The doctor is likely to conduct further diagnostic procedures to rule out other conditions that could cause similar symptoms, such as asthma or, especially in smokers, LUNG CANCER.

Treatment Options and Outlook

Treatment for acute viral bronchitis is primarily supportive and targets symptom relief. The doctor may recommend a cough suppressant or an OVER-THE-COUNTER (OTC) DRUG such as acetaminophen to relieve fever and discomfort. It is important to drink lots of fluids to maintain HYDRATION and to thin bronchial secretions. When fever persists or recurs after acute infectious bronchitis, the likelihood of bacterial infection is high in which case treatment with ANTIBIOTIC MEDICATIONS becomes necessary. Antibiotics are not helpful for viral bronchitis, however. The doctor may prescribe an inhaled corticosteroid medication to suppress the inflammatory response in acute irritative bronchitis. Bronchodilators may also help if the bronchitis causes bronchospasm and wheezing.

The most effective treatment for chronic bronchitis is removing the cause of the symptoms, which most often is cigarette smoking. Chronic bronchitis becomes inevitable at some point in everyone who smokes. People who work in environments with high exposures to fumes, dust, or pollutants should use appropriate protective gear including masks or respirators. Chronic bronchitis that continues unchecked results in permanent damage to the bronchial structures.

Risk Factors and Preventive Measures

Frequent HAND WASHING is the best defense against viral infections of any sort. Upper respiratory viruses spread through droplet contamination, which may occur through direct touch (such as shaking hands) or breathing droplets coughed or sneezed into the air by those who have upper respiratory viruses. In epidemic circumstances, doctors may prescribe antiviral medications such as rimantadine to reduce the risk or severity of infection. Removal from the source of irritation reduces symptoms to improve chronic bronchitis. People who have high risk of respiratory infection, such as those who have chronic lung disease or other chronic health conditions, should receive influenza vaccination (flu shot) every year and pneumonia vaccination every five years.

See also ANTIBIOTIC RESISTANCE; CROUP; HEMOPTYSIS; PNEUMONITIS; SMOKING AND PULMONARY DISEASE.

bronchoalveolar lavage A diagnostic procedure that washes cells from the bronchi and alveoli for laboratory examination. The doctor does bronchoalveolar lavage during BRONCHOSCOPY, blocking a small section of the bronchial segment to instill and then withdraw sterile saline. The solution contains cells from the inner lung structures that can provide diagnostic information. The doctor may also use bronchoalveolar lavage therapeutically, to irrigate (rinse away) thickened mucus or other deposits from the LUNGS in conditions when thick plugs of mucus block the airways and do not respond to other treatments.

See also ALVEOLUS; BRONCHUS.

bronchoscopy A diagnostic procedure in which the doctor uses a flexible, lighted endoscope, inserted through the THROAT and into the airways under sedation or ANESTHESIA, to view the TRACHEA, bronchi, and other structures of the respiratory tract. The doctor also can watch the LUNGS in motion, assessing air movement and filling. Bronchoscopy is an outpatient procedure that takes about an hour. Many people receive mild sedation before the bronchoscopy to help them relax and be more comfortable.

The bronchoscope is a thin, flexible, lighted tube with a tiny camera on the tip. The pulmonologist sprays a topical anesthetic on the back of the throat to block the GAG REFLEX and numb the throat, then inserts the bronchoscope through the MOUTH (or the NOSE, with lubrication) and throat into the trachea. The pulmonologist guides the bronchoscope into the bronchi, which enables examination of the lung to a moderate depth of about four or five branchings of the bronchus. The pulmonologist may use bronchoscopy to obtain tiny tissue samples for biopsy or to perform BRONCHOALVEOLAR LAVAGE to obtain bronchial and alveolar cell samples. Bronchoscopy may also be therapeutic, allowing the pulmonologist to rinse accumulated mucus and debris from the bronchi.

It is common to feel some discomfort after the topical anesthetic wears off, similar to a sore throat. The discomfort generally does not last more than a day or two. Rarely after a biopsy, bronchoscopy may cause a PNEUMOTHORAX, a condition in which air gets in the pleural space (a small area around the lung) and the lung collapses. The risks of bronchoscopy for most people are minimal.

See also ALVEOLUS; BRONCHUS; ENDOSCOPY.

bronchus A secondary branch of the airways that connect the LUNGS and the primary airway, the TRACHEA. The main bronchi branch directly from the trachea at about mid-lung, with the right main bronchus channeling air to the right lung and the left main bronchus directing air to the left lung. Each main bronchus nearly immediately branches into lobular bronchi, three in the right lobe and two in the left lobe. Bronchi become diminishingly smaller as they branch deeper into the lungs. Rings of CARTILAGE give larger bronchi rigidity and support. Smaller bronchi have fewer and thinner cartilage rings, and bronchioles, the tiniest of the bronchi, have thin walls of only

smooth MUSCLE tissue with no cartilage. The bronchi are susceptible to irritation, INFLAMMATION, and INFECTION. When inflamed or irritated the bronchi can cause difficulty breathing (DYSPNEA).

For further discussion of the bronchi within the context of pulmonary structure and function please see the overview section "The Pulmonary System."

See also ALVEOLUS; ASTHMA; BRONCHIECTASIS; BRONCHITIS.

byssinosis A lung disorder resulting from extended exposure to the dust from cotton, flax, or other textile fibers. Also called brown lung, cotton worker's lung, or cotton bract disease, byssinosis is an occupational disease that causes ASTHMA-like symptoms. When detected in its early stages, byssinosis is reversible by eliminating exposure to the responsible irritant. When exposure continues the byssinosis can cause permanent damage to the LUNGS with symptoms similar to those of CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD). In the United States people who work in jobs where they handle unprocessed cotton have the highest risk of developing byssinosis.

The symptoms of byssinosis tend to be worse at the workplace and improve away from the workplace and typically include wheezing and coughing. The diagnostic path focuses on the work history and includes X-rays of the chest and tests to assess pulmonary capacity and function. The most effective treatment is preventing continued exposure, which may involve workplace improvements or changing jobs. Medications to reduce the HYPERSENSITIVITY REACTION the airways have to the fiber dust, such as bronchodilators and sometimes CORTICOSTEROID MEDICATIONS, can relieve or prevent symptoms. Smoking significantly exacerbates byssinosis, so SMOKING CESSATION is crucial to other treatment approaches.

See also ASTHMA; BERYLLIOSIS; OCCUPATIONAL HEALTH AND SAFETY; SARCOIDOSIS; SILICOSIS.

C–E

chest percussion and postural drainage A therapeutic method for loosening and clearing mucus from the LUNGS, used especially in CYSTIC FIBROSIS and BRONCHIECTASIS, when there is ATELECTASIS, and in other pulmonary disorders in which mucus collects and blocks the flow of air. For this treatment, a respiratory therapist or caregiver trained in the method rhythmically claps, with cupped hands, on the SKIN surfaces of the chest and back over the thoracic cavity with the person receiving the treatment in various postures, depending on the location of the clapping. The therapist may choose to use a mechanized percussor instead of the hands, which allows longer and more intensive percussion.

Clapping over the upper chest (near the collarbones) and upper back (near the shoulder blades) loosens secretions in the upper lobes. Clapping over the midchest (nipple line) and midback loosens secretions in the middle lobes. Clapping over the lower chest (below the nipple line) and lower back loosens secretions in the lower lobes. Precise positioning of the hands when clapping can further target specific segments of the lobes. The percussion of the clapping loosens mucus and secretions within the bronchi, which the person then coughs up to remove from the respiratory tract.

See also COUGH; CYSTIC FIBROSIS AND THE LUNGS.

Cheyne-Stokes respiration A pattern of BREATHING in which periods of APNEA alternate with periods of accelerated breathing. Cheyne-Stokes respiration indicates damage to the brainstem or other NERVOUS SYSTEM mechanisms that regulate breathing. This breathing pattern also occurs in severe HEART FAILURE. During the apneic periods, which may last up to 60 seconds, breathing stops. During the accelerated periods, the RESPIRATORY RATE rapidly increases in rate and depth (hyperpnea) then abruptly stops as the cycle returns to apnea. Cheyne-Stokes respiration may reflect an end-stage (near death) breathing pattern in adults, though may persist for an extended time in people who are comatose.

See also DYSPNEA; TACHYPNEA.

chronic obstructive pulmonary disease (COPD) A serious, often debilitating, and potentially fatal condition in which INFLAMMATION and scarring destroy alveoli, bronchioles, and bronchi. The most common cause of COPD is cigarette smoking; 8 of 10 Americans who have COPD are smokers. Uncontrolled ASTHMA and chronic lung diseases such as ASBESTOSIS and SILICOSIS can also progress to COPD. About 16 million people in the United States have COPD and more than 100,000 of them die from it each year.

COPD takes years to decades to develop, and its damage is permanent. The most common presentation is that of chronic BRONCHITIS, in which there is repeated inflammation of the bronchi. Each bout of inflammation results in the formation of SCAR tissue as the damaged area heals. Over time the scar tissue causes the bronchi to narrow, with areas of constriction that severely limit the flow of air. ATELECTASIS (collapse) may occur in affected bronchial structures, reducing the ability of the lung to diffuse oxygen into the bloodstream.

In about 10 percent of people who have COPD the damage extends to the alveoli, the clusters of air sacs where oxygen–carbon dioxide exchange takes place. Repeated inflammation and scarring causes the alveoli to enlarge and lose elasticity, a state called emphysema. The damaged alveoli can take in air but cannot collapse sufficiently to expel

the air completely. A rare form of emphysema is an inherited deficiency of the enzyme alpha-1-antitrypsin (AAT), which regulates the presence of elastin in the tissues of the alveoli. AAT deficiency results in reduced elastin, further limiting alveolar function. Because of the intimate correspondence between the capillary BLOOD supply and alveolar oxygen content, blood supply shifts away from damaged alveoli.

The ultimate damage of COPD, regardless of whether the primary course of disease started as bronchial or alveolar, is so profound that both dimensions of damage eventually overtake the LUNGS and the lungs lose the ability to recoil (return to their normal shape and size), diminishing the ability to exhale. Consequently, people who have COPD can breathe in with relative ease but struggle to move air back out of their lungs. People who have moderate to advanced COPD typically exhale through pursed lips, an effort to more forcefully exhale. Even with this effort, the person may be unable to blow out a match.

As the disease process progresses the less elastic lungs expand within the thoracic cavity, pushing the ribs out and the DIAPHRAGM down to produce a characteristic barrel chest deformity. However, these structural changes further limit the ability of the diaphragm and intercostal muscles to expand the chest for inhalation, restricting the ability of the lungs to draw in air. This generates a characteristic posture adaptation in which the person leans forward to use other muscles in the neck and shoulders to assist with BREATHING. Ordinary movements such as raising the arms (such as to wash or brush the hair) consequently cause shortness of breath because such movements reduce the involvement of these ancillary muscles. In its later stages COPD affects both inhalation and exhalation.

Symptoms and Diagnostic Path

The symptoms of COPD include

- progressive DYSPNEA (shortness of breath)
- wheezing (whistling sounds with exhalation)
- persistent, productive COUGH
- HEMOPTYSIS (bloody SPUTUM)
- edema (swelling due to fluid retention) in the feet, ankles, and lower legs
- CYANOSIS (bluish hue to the lips and SKIN that signals inadequate oxygenation)
- physical signs characteristic of COPD (barrel chest, purse-lip breathing, forward-leaning posture) when emphysema is dominant
- current or previous cigarette smoking

The diagnostic path includes a complete pulmonary workup to evaluate lung capacity and function, which typically show significant reductions. Chest X-rays and COMPUTED TOMOGRAPHY (CT) SCAN show the extent of damage to the lungs as well as displacement of the thoracic structures. The doctor typically does sputum cultures to identify or rule out INFECTION. Diagnostic blood tests often show an elevated ERYTHROCYTE (red blood cell) count particularly in people who have low oxygen levels, indicative of the body's attempt to improve the oxygen-carrying ability of the blood. Diagnostic efforts focus on ruling out other possible causes for symptoms as well as correlating physical findings with history of smoking.

CLASSIFICATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Classification	Severity	Symptoms
stage 0	at risk	smokes but has no COPD symptoms
stage 1	mild	chronic COUGH
stage 2	moderate	chronic, productive cough DYSPNEA with exertion
stage 3	severe	chronic, productive cough excessive SPUTUM dyspnea at rest right HEART FAILURE common

Treatment Options and Outlook

The most important element of treatment is SMOKING CESSATION. Although it is not possible to reverse damage that has already occurred, treatment aims to minimize further lung damage and improve function of the remaining lung. Medications such as bronchodilators relax and open the airways,

easing the flow of air in and out of the lungs. CORTICOSTEROID MEDICATIONS reduce inflammation and in some people may also help open the airways. When infection is present, the doctor may prescribe ANTIBIOTIC MEDICATIONS. However, people who have COPD often have extensive bacterial flora, making it difficult for the doctor to determine whether there is an actual infection present. People who have COPD should receive annual INFLUENZA immunizations and PNEUMONIA vaccination every five years. As with all lung diseases, it is important to minimize as much as possible other triggers: SINUSITIS, GASTROESOPHAGEAL REFLUX DISORDER (GERD), and exposure to known ALLERGENS.

For some people surgery to remove the upper lobes of the lungs, called lung volume reduction surgery (LVRS), relieves tension within the thoracic cavity and improves pulmonary function and overall lung capacity. LUNG TRANSPLANTATION may be a viable treatment option for some people, replacing one of the diseased lungs with a donor lung. The criteria for these procedures are stringent and take into account numerous health and lifestyle factors.

Nutritional support is essential for people with advanced COPD, who typically lose significant body weight as the effort to breathe requires intense work from numerous muscles. Regular physical exercise is also important. Though breathing with exertion may severely limit the duration of activity, maintaining physical STRENGTH allows the body to make the most of the available oxygen the lungs can diffuse into the bloodstream. Many hospitals have pulmonary rehabilitation programs with specialists who can teach targeted exercises to improve AEROBIC FITNESS and MUSCLE strength. For many people pulmonary rehabilitation is as effective as any surgical alternatives. Walking remains one of the most effective activities.

Complications of COPD are common, particularly in the later stages. Typical complications include HEART FAILURE, PULMONARY HYPERTENSION and RESPIRATORY FAILURE. Doctors sometimes refer to the combination of right-heart failure and pulmonary hypertension as cor pulmonale. People who have COPD are particularly vulnerable to viral infections such as COLDS and influenza, and often develop secondary bacterial infections such as pneumonia and acute bronchitis.

Risk Factors and Preventive Measures

The leading risk factor for COPD is cigarette smoking. The most effective preventive measure is never to smoke and to avoid exposure to secondhand smoke (ENVIRONMENTAL CIGARETTE SMOKE). Smoking cessation can improve lung capacity and function, though cannot undo damage that has already occurred. Prompt and appropriate treatment of other pulmonary conditions, such as asthma, helps minimize permanent damage that could set the stage for COPD to subsequently develop. Though COPD occurs primarily in people over age 40, this is a consequence of cumulative damage to the lungs over time rather than aging.

See also BRONCHITIS; LIVING WITH CHRONIC PULMONARY CONDITIONS; PNEUMOTHORAX; SMOKING AND PULMONARY DISEASE.

collapsed lung See ATELECTASIS.

cystic fibrosis and the lungs An inherited genetic disorder affecting mucus production and clearance, CYSTIC FIBROSIS alters the functioning of exocrine glands throughout the body and affects nearly all of the body's systems. In the LUNGS, cystic fibrosis causes changes in the consistency and composition of the mucus the lungs secrete. The mucus accumulates along the inner walls of the bronchi, causing irritation and INFLAMMATION that eventually thickens the walls of the bronchi. The mucus becomes thick, creating obstructions in the bronchi that reduce air flow and eventually produce regions of ATELECTASIS (collapsed bronchial segments). The plugs of thickened mucus also attract BACTERIA, resulting in recurrent INFECTION that manifest as BRONCHITIS and PNEUMONIA.

Health experts estimate that about 3 percent of the population in the United States carries the recessive GENE MUTATION for cystic fibrosis. The disorder is 5 to 10 times more common among whites than among other racial populations. Even one generation ago, cystic fibrosis typically caused death by late ADOLESCENCE. Current treatment methods and early diagnosis has extended life expectancy into the 30s for most people who have cystic fibrosis, and many live longer. Cystic fibrosis nearly always affects the lungs and requires continuous therapy to maintain adequate BREATHING and oxygenation.

Symptoms and Diagnostic Path

The symptoms of cystic fibrosis vary according to the body system first affected and usually appear in childhood. Chronic productive COUGH, recurrent bronchitis or pneumonia, and pronounced wheezing are among the indications of pulmonary involvement. The diagnostic path includes chest X-rays and pulmonary function tests, which demonstrate changes in lung structure and function characteristic of cystic fibrosis. Other diagnostic procedures look for nonpulmonary indications of cystic fibrosis such as sinus disease, pancreatic disease, decreased BONE DENSITY, and INFERTILITY. Family history of cystic fibrosis provides strong suspicion of the diagnosis. A positive sweat chloride test and GENETIC TESTING that identifies cystic fibrosis mutations. This provides conclusive diagnosis.

Treatment Options and Outlook

Treatment requires close coordination to target symptoms and disease developments across body systems. Pulmonary treatment aims to keep the airways as open as possible and to prevent infection, or treat infection early and aggressively. IMMUNIZATION to protect against CHILDHOOD DISEASES such as PERTUSSIS (whooping cough), CHICKENPOX, and MEASLES are crucial, as are annual INFLUENZA immunizations (flu shots) and pneumonia vaccination every five years at all ages. CHEST PERCUSSION AND POSTURAL DRAINAGE help clear the airways of mucus accumulations. Though coughing is a frustrating symptom, it is also an important function for removing mucus from the chest. Bronchodilators help improve functioning of the airways and removal of mucus from them.

Moderate to high doses of the NONSTEROIDAL ANTI-INFLAMMATORY DRUG (NSAID) ibuprofen (Advil or Motrin) taken regularly may slow bronchial inflammation and damage in many people, especially children. CORTICOSTEROID MEDICATIONS become necessary when ibuprofen can no longer control the inflammation or when inflammation becomes widespread in the lungs. ANTIBIOTIC MEDICATIONS become necessary to treat infections. People who have cystic fibrosis commonly acquire antibiotic-resistant bacteria, which may necessitate treatment with more powerful intravenous antibiotics. Inhaled antibiotic therapies are also becoming available for treatment as well as prophylaxis (prevention).

Cystic fibrosis has numerous nonpulmonary complications that also require close attention. Dysfunction of the PANCREAS results in malabsorption that may necessitate nutritional support. The nature and severity of symptoms vary widely among individuals. Cystic fibrosis is progressive, however, and these treatments are only supportive. When they fail, bilateral LUNG TRANSPLANTATION is the final, though high-risk, treatment option.

Risk Factors and Preventive Measures

The only risk factor for cystic fibrosis is the recessive gene mutation. Because this mutation is relatively prevalent in the American population, many people do not know they carry it until a child develops the disease. Genetic testing and GENETIC COUNSELING may be helpful for people who have family histories of cystic fibrosis.

See also ANTIBIOTIC PROPHYLAXIS; ANTIBIOTIC RESISTANCE; GENETIC DISORDERS; INHERITANCE PATTERNS; ORGAN TRANSPLANTATION.

diaphragm The thin, flat MUSCLE that forms the floor of the thoracic cavity (chest), establishing a physical barrier between the thoracic cavity and the abdominal cavity. Small openings in the diaphragm allow structures such as the AORTA, inferior VENA CAVA, and ESOPHAGUS to pass through. The lower lobes of the LUNGS and the base of the HEART rest against the diaphragm. The diaphragm attaches to the lower ribs and spine in the back, then rises along the back of the ribs to dome forward to form the base of the thoracic cavity. Contraction of the diaphragm tightens this dome, pulling it downward to expand the thoracic cavity. The diaphragm has two equal halves, each called a hemidiaphragm, and is the primary muscle of BREATHING.

Health conditions that can involve the diaphragm include HIATAL HERNIA, in which weakness in the musculature around the esophageal opening allows the stomach to bulge upward through the opening. Hiatal hernia typically causes an uncomfortable burning sensation and may result in regurgitating food or GASTROESOPHAGEAL REFLUX DISORDER (GERD). HICCUPS are muscle spasms of the diaphragm.

THE HEIMLICH MANEUVER

The HEIMLICH MANEUVER, an emergency procedure for ejecting an inhaled object from the TRACHEA, uses the DIAPHRAGM to generate a forceful exhalation. Placing a sharp, upward thrust into the diaphragm causes the diaphragm to rapidly contract and relax, sending its dome higher into the thoracic cavity than usual. The effect strongly compresses the LUNGS, forcing them to propel air outward. The force of the air dislodges the object.

For further discussion of the diaphragm within the context of pulmonary structure and function please see the overview section "The Pulmonary System."

See also BREATHING EXERCISES.

dyspnea Difficulty BREATHING or shortness of breath. There are numerous causes of dyspnea, most of which relate to cardiovascular or pulmonary disorders. Dyspnea occurs when the body does not receive enough oxygen. As oxygen is the fuel for cellular activity, lack of oxygen means cells cannot function properly. When oxygen insufficiency (HYPOXIA) is systemic (involves all the body) the body begins to conserve oxygen for vital uses. This concurrently slows activity of nonessential cells such as skeletal MUSCLE cells and sends signals to the LUNGS and HEART to increase their productivity.

Dyspnea may occur as a result of intense physical activity, such as exercise, in which case it generally diminishes with improved AEROBIC FITNESS. Dyspnea associated with cardiovascular or pulmonary disease may lessen slightly with pulmonary rehabilitation and improved physical conditioning but typically does not improve substantially unless the underlying disease condition improves. CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) and HEART FAILURE are the two most common causes of dyspnea. Doctors assess clinical dyspnea according to the degree to which it interferes with normal activities.

See also APNEA; ASPHYXIATION; DISABILITY AND EXERCISE; INTERSTITIAL LUNG DISORDERS; LIVING WITH CHRONIC PULMONARY CONDITIONS.

emphysema See CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD).

GRADES OF DYSPNEA

Grade	Severity	Level of Impairment
grade 1	minimal	shortness of breath with exertion such as climbing multiple flights of stairs, short running such as to catch a bus, or walking uphill
grade 2	mild	shortness of breath with moderate exertion such as climbing a single flight of stairs or walking several blocks on the flat
grade 3	moderate	shortness of breath with mild exertion such as walking one block on the flat; must pause when climbing a single flight of stairs
grade 4	significant	shortness of breath with everyday physical activity; must pause when walking on the flat; must pause every few steps when climbing a flight of stairs
grade 5	incapacitating	shortness of breath with any physical effort including dressing, undressing, showering or bathing; cannot walk more than a few steps without pausing; cannot climb steps

H–I

hemoptysis Bleeding from the LUNGS, which typically manifests through BLOOD in the SPUTUM. Hemoptysis is typically frothy and bright red, though can sometimes be difficult to distinguish from blood that might originate in the ESOPHAGUS or STOMACH.

Hemoptysis that produces a volume of blood greater than the equivalent of two or three teaspoonfuls is a medical emergency that may represent hemorrhage and requires immediate treatment.

Hemoptysis is a symptom of numerous health conditions affecting the lungs, and may appear as blood-streaked sputum or primarily blood with little apparent sputum present. The diagnostic path includes chest X-rays, blood tests, and sputum cultures. Lung hemorrhage is a surgical emergency that generally requires immediate intervention to locate and stop the source of bleeding, commonly a perforated ARTERY. Treatment for less severe bleeding focuses on the underlying cause. The most common cause overall of hemoptysis is BRONCHITIS.

COMMON CAUSES OF HEMOPTYSIS

BRONCHIECTASIS	BRONCHITIS
CYSTIC FIBROSIS	LUNG CANCER
PNEUMONIA	PULMONARY EMBOLISM
TUBERCULOSIS	violent coughing
Wegener's granulomatosis	

See also ANEMIA; GASTROINTESTINAL BLEEDING.

hiccups Dysfunctional or out-of-sequence contractions (spasms) of the DIAPHRAGM. Hiccups generally occur rhythmically in episodes that typically contain four to several dozen contractions. An individual tends to have a personally consistent pattern. Though doctors know the mechanics of hiccups, no one knows what causes hiccups or what, if any, purpose they serve. For most people hiccups are nothing more than an annoyance. However, prolonged attacks can have health consequences.

There is no certain cure for hiccups, though recommended remedies are abundant. Some remedies, such as swallowing a spoonful of sugar or sniffing an ammonia capsule, irritate the airways. Swallowing ice water may activate nerves in the ESOPHAGUS that diffuse the NERVE impulses causing the diaphragm to contract. BREATHING into a paper bag raises the percentage of carbon dioxide in the BLOOD, which alters the brain signals to the diaphragm. It is important that any prospective cure carry little risk of causing harm.

Doctors may treat persistent hiccups with medications that are mildly sedating, such as antiseizure or anticholinergic medications. A mild anesthetic may slow the signals from the brainstem. Mild MUSCLE relaxants and tricyclic antidepressants are also successful in some people. Extended hiccups may result in vasovagal nerve irritation that causes ARRHYTHMIA (irregularities in the heartbeat). In most circumstances of prolonged hiccups, treating underlying health conditions stops the hiccups.

See also HYPERVENTILATION; MYOCLONUS; SPASM.

hyperventilation Rapid, shallow BREATHING that causes carbon dioxide levels in the BLOOD to drop below normal. As the balance between carbon dioxide and other gases in the blood is essential for normal pulmonary and cardiovascular func-

tion, the decrease triggers actions in the body designed to slow the breathing. Key among these is temporary loss of consciousness (fainting), which returns breathing to the involuntary control of the brainstem and restores normal breathing patterns. People who are hyperventilating often feel as if they were not getting enough oxygen, though in fact they are getting plenty. Most often hyperventilation results from emotional stress, panic, or anxiety. Rarely, cardiovascular or pulmonary disturbances cause a similar breathing pattern. Chest X-RAY, blood tests, and ELECTROCARDIOGRAM (ECG) can quickly determine whether this is the case.

The standard treatment for an active episode of hyperventilation is breathing slowly and purposefully. Breathing through only one nostril (holding the other nostril closed with the fingers) helps focus conscious intent on the breathing as well as reduce the amount of air entering the LUNGS.

Though once a common remedy for hyperventilation, BREATHING into a paper bag may allow carbon dioxide levels in the blood to rise too much. Doctors no longer recommend this method.

Once breathing returns to normal the oxygen–carbon dioxide balance in the blood does the same and symptoms such as dizziness or lightheadedness fade. Stress management methods such as MEDITATION and YOGA help lower overall anxiety levels, which reduces hyperventilation episodes. BREATHING EXERCISES are also helpful. Hyperventilation without underlying cardiovascular or pulmonary disease is not harmful to health.

See also HYPOXIA.

hypoxemia See OXYGEN SATURATION.

hypoxia Inadequate oxygen perfusion of the tissues. Hypoxia occurs when the BLOOD cannot deliver adequate oxygen, which may result from pulmonary dysfunction, cardiovascular dysfunction, STROKE, TRAUMATIC BRAIN INJURY (TBI), disorders of the blood such as ANEMIA that affect erythrocytes (red blood cells) or HEMOGLOBIN, and BREATHING disturbances such as APNEA. Hypoxia may involve only a defined organ or area, such as a region of the BRAIN affected by STROKE, or involve the entire body. Permanent tissue damage or tissue death results when hypoxia persists. Symptoms of hypoxia may include CYANOSIS (bluish hue to the lips and SKIN), tiredness, and DYSPNEA (shortness of breath or difficulty breathing). Most hypoxia requires supplemental oxygen with additional treatment that targets the underlying cause.

See also ALTITUDE SICKNESS; DECOMPRESSION SICKNESS; OXYGEN SATURATION; OXYGEN THERAPY; POLYCYTHEMIA VERA.

interstitial lung disorders A broad term for chronic conditions that restrict the ability of the LUNGS to function properly, encompassing more than 150 diseases. Interstitial lung disorders, also called interstitial lung disease as a collective term, are typically obstructive, fibrotic (involve SCAR formation), and progressive. Many arise from occupational exposures such as to asbestos (ASBESTOSIS), silica (SILICOSIS), and coal dust (miner's PNEUMONOCONIOSIS). A variant form that more commonly occurs later in life, idiopathic pulmonary fibrosis (IPF), has no identifiable cause and tends to be more severe in its progression.

The general symptoms, diagnostic paths, and treatment approaches are similar for interstitial lung disorders. Common symptoms include COUGH, DYSPNEA (shortness of breath or difficulty BREATHING), and frequent INFECTION. Treatment targets slowing the progression of the disease, relieving symptoms, and preventing infections. Lung transplantation is sometimes a treatment option for severely progressive IPF. However, many people who have interstitial lung disorders are able to manage their symptoms for years to decades, allowing satisfactory QUALITY OF LIFE.

See also CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD); CYSTIC FIBROSIS AND THE LUNGS; LIVING WITH CHRONIC PULMONARY CONDITIONS.

L–M

Legionnaires' disease A serious and potentially fatal form of PNEUMONIA first identified in 1976 when several hundred people attending a Legionnaires' convention became ill, a number of whom died as a result of the INFECTION. Scientists subsequently isolated the causative bacterium *Legionella pneumophila*. The BACTERIA infect about 18,000 people in the United States each year, about 4,000 of whom die from the disease or its complications. A less severe form of the infection with the same bacteria is Pontiac FEVER, which presents milder forms of similar symptoms (though without subsequent complications). Health experts refer to these infections collectively as legionellosis. Heating and cooling systems in buildings can harbor *L. pneumophila*, which then spread the bacteria through ventilation networks. Frequent and diligent cleaning of these systems is the most effective means for limiting outbreaks of infection.

Symptoms and Diagnostic Path

Legionnaires' disease begins as a typical viral upper-respiratory infection with symptoms that begin 3 to 10 days after exposure and include fever, generalized aches and discomfort, loss of APPETITE, HEADACHE, fatigue, and COUGH. Some people also have gastrointestinal symptoms such as diarrhea. Within a week the symptoms worsen to include coughing up SPUTUM, chest tightness or PAIN, and DYSPNEA (shortness of breath). Some people also experience multiple neurologic symptoms, including confusion and cognitive dysfunction.

A chest X-RAY shows signs of pneumonia, and diagnostic blood tests often show indications of infection in the body. The doctor may order specialized tests to detect the presence of *L. pneumophila* in the sputum or of *L. pneumophila* antigens in the URINE. A key factor in suspecting Legionnaires' disease is knowing the possibility of exposure, either because others have become ill or because the person was at an event at a setting conducive to transmitting Legionnaires' disease, such as a large convention. Other water sources as well as respiratory equipment in hospitals harbor *L. pneumophila,* which has become a common cause of community-acquired pneumonia as well as of NOSOCOMIAL INFECTIONS (hospital-acquired infections).

Treatment Options and Outlook

The primary treatment for Legionnaires' disease is hospitalization for intravenous therapy with the ANTIBIOTIC MEDICATIONS of the macloide or fluoroquinoline class (such as azithromycin or levofloxacin). Illness in some people is mild enough to allow outpatient treatment with oral antibiotics, though others may require hospitalization. As with any severe infection, multiple system failure is a significant risk in people who already have other major health conditions such as CARDIOVASCULAR DISEASE (CVD), DIABETES, or pulmonary disorders. Early diagnosis and treatment are critical; the likelihood of death resulting from the infection increases dramatically when people delay seeking medical care or doctors are unaware of the possibility of the diagnosis. Among people who are otherwise healthy, have normal immune function, and receive prompt treatment, more than 95 percent recover. However, many people continue to have some symptoms, such as fatigue, for several months.

Risk Factors and Preventive Measures

Infection with *L. penumophila* can occur in several venues. People who already have some form of pulmonary compromise, such as ASTHMA or CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD),

seem more likely to contract Legionnaires' disease than people who have healthy lung function with equal exposure to a contaminated source. People who smoke have the highest risk, whether or not they have underlying pulmonary disease. People between the ages of 50 and 70 seem most likely to develop infection after exposure.

The most effective preventive measure is strict maintenance and cleaning of building air-conditioning and heating systems, spas, whirlpools, and other potential sources of culture for the bacteria. Heightened awareness about Legionnaires' disease has resulted in improved diligence. The US Occupational Safety and Health Agency (OSHA) has implemented guidelines for building maintenance. Because the bacteria enter the upper respiratory tract during breathing, there are few personal measures to reduce the risk for infection as often it is not possible or practical to avoid locations that are potential sources of infection.

See also INDOOR AIR QUALITY.

living with chronic pulmonary conditions More than 30 million Americans live with chronic pulmonary conditions such as ASTHMA, CYSTIC FIBROSIS, PULMONARY FIBROSIS, and CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD). Though many chronic pulmonary conditions are far more common among people over age 50, chronic pulmonary disease affects young people too. Chronic pulmonary disease requires most people to make accommodations in their lifestyles, recreational activities, and occupations.

Medical Care

People who have chronic pulmonary conditions require ongoing medical surveillance and treatment such that they may feel they "live at the doctor's office." They often take numerous medications and receive respiratory therapy treatments. Many undergo frequent hospitalizations for attacks, exacerbations, and INFECTION. Compliance with medical treatments plan is essential but not always easy. It is common to feel that medications are no longer necessary when they bring about significant improvement, yet taking medications as prescribed is the most effective way to prevent complications and, in many situations, slow or halt the condition's progress.

Self Care

Various lifestyle factors influence the course of chronic pulmonary conditions. Some are actions a person can and should take to improve his or her pulmonary status. Other actions target overall health and well-being. It is important for each person to take leadership of his or her health and care.

Cigarette smoking Cigarette smoking is the most significant factor in many forms of chronic pulmonary disease. The optimal lifestyle choice for healthy lungs is never to start smoking; the next best decision is to stop smoking. Though it is not often possible to undo damage that has already occurred to the LUNGS, smoking cessation can result in improvement no matter when it takes place.

Breathing exercises BREATHING is such a natural occurrence that few people give it a second thought until it becomes a struggle. BREATHING EXERCISES can increase lung capacity and efficiency, teaching ways to get the most from every breath of air.

Nutritious eating habits Working hard simply to breathe requires a lot of calories. For people who have severe pulmonary conditions, breathing can commandeer most of the calories consumed each day. It is important to get enough calories to meet the body's needs and to infuse the body with vital NUTRIENTS that support health and HEALING.

Regular exercise When simply breathing consumes most of the body's energy, it's easy to slack off exercise. Yet the body requires regular physical activity to function at its most efficient. Though chronic pulmonary conditions often limit physical exertion, many activities remain possible with adaptation. Walking is among the most effective exercises, providing AEROBIC FITNESS as well as strengthening muscles. Some people find the relative weightlessness of swimming allows them to do more with less effort. Nearly everyone, regardless of disease type or stage, can engage in small activities that improve the body's fitness. Structured pulmonary rehabilitation programs help people to make the most of the lung function they do have.

Mental health and emotional balance Coping with the challenges and setbacks of chronic health conditions can be overwhelming. Children who have chronic pulmonary conditions may struggle with peer acceptance and feeling left out of school and social activities. Some people find support groups safe ways to express anger, fear, and worry,

as well as to share information and experiences. Other people take comfort in the solitude of prayer or MEDITATION. Stress relief methods such as YOGA and VISUALIZATION help recenter the thoughts and the mind.

Looking to the Future

Though chronic pulmonary conditions are often limiting or debilitating, many people are able to participate in activities they enjoy. With appropriate medical care and self-care, a long and productive life is not only possible but probable for many people who have chronic pulmonary conditions.

See also LIFESTYLE AND HEALTH; QUALITY OF LIFE.

lung abscess A pocket of INFECTION deep within the lung that isolates itself within a defined area of the lung (having a clear boundary between the infected tissue and the healthy tissue), usually behind a blocked segment of BRONCHUS. A lung abscess often follows a known bacterial INFECTION such as PNEUMONIA or BRONCHITIS in which INFLAMMATION or excessive mucus blocks an airway, though may occur without an obvious precipitating infection. A lung abscess may cause COUGH, chest discomfort or PAIN, chills, bouts of profuse sweating (diaphoresis), and difficulty BREATHING (DYSPNEA). Chest X-RAY or COMPUTED TOMOGRAPHY (CT) SCAN allows the doctor to visualize the location and size of the abscess. Cultured SPUTUM samples often provide evidence of the infective PATHOGEN. Treatment with ANTIBIOTIC MEDICATIONS successfully eradicates most lung abscesses. Sometimes the abscess requires drainage, which the doctor often can do by placing a drain through the skin. Occasionally OPEN SURGERY is necessary to open and clean the abscess, and to débride (trim away) damaged or dead tissue surrounding the abscess. Most people heal completely and without complication with appropriate treatment. An untreated lung abscess can result in serious health consequences including significant loss of lung tissue or SEPTICEMIA (total body infection, also called sepsis).

See also ATELECTASIS; BRONCHIECTASIS.

lung cancer Malignant tumors that grow in the LUNGS. Lung CANCER may be primary (originate in the lungs) or metastatic (spread to the lungs from cancer that originates elsewhere in the body). There are two main types of lung cancer: small cell lung cancer (SCLC), which is particularly aggressive, and non–small cell lung cancer (NSCLC). Malignant mesothelioma is a specific kind of cancer that arises from asbestos exposure. Cigarette smoking causes 87 percent of lung cancer in the United States and nearly all SCLC. Other causes of lung cancer include exposure to carcinogenic (cancer-causing) substances such as radon (the second-leading cause of lung cancer) and asbestos (which, when combined with smoking, compounds the risk for lung cancer).

Doctors diagnose 175,000 people with lung cancer in the United States each year. Lung cancer is the leading cause of death from cancer among men and women alike, taking the lives of 160,000 Americans each year and accounting for 30 percent of all deaths from cancer. The five-year SURVIVAL RATE is about 14 percent, which is very low compared to many other kinds of cancer. A key reason lung cancer is so frequently fatal is that it does not show symptoms until it is quite advanced, making treatment difficult. Doctors are able to diagnose only 15 percent of lung cancers when the initial tumor remains localized (confined to a distinct site within the lung), a point in time where intervention could vastly improve the chance of survival.

Non–Small Cell Lung Cancer (NSCLC)

About 80 percent of lung cancer is NSCLC. There are three types of NSCLC:

- ADENOCARCINOMA, which arises from the mucus-secreting cells in the bronchial structures
- squamous cell CARCINOMA, which arises from the epithelial cells that form the inner lining of the airways
- large cell carcinoma, which commonly originates in the bronchi and contains neither squamous cells nor adenomatous (glandular) cells

Staging and treatment protocols are the same across the types of NSCLC. The most common type of NSCLC is adenocarcinoma, which is moderately aggressive. Large cell carcinoma, which accounts for about 20 percent of NSCLC, tends to be more aggressive than other NSCLC tumors and larger and metastasized at the time of diagnosis.

BASIC STAGING OF NON–SMALL CELL LUNG CANCER (NSCLC)

Stage	Extent of Cancer	Treatment Protocols/Options
stage 0	cancer cells are present only in the lining of the bronchi (carcinoma in situ)	surgery or local therapy
stage 1a	tumor is less than 3 centimeters (cm), does not involve a major BRONCHUS, and has not spread beyond the site of origin	surgery (lobectomy) possible adjuvant RADIATION THERAPY
stage 1b	tumor may be more than 3 cm, may have spread to the PLEURA, or partially blocks a bronchus but has not spread to LYMPH NODES	surgery (lobectomy) probable adjuvant radiation therapy
stage 2a	tumor is less than 3 cm and has spread to adjacent lymph nodes but not to the pleura or sites beyond the lung	surgery (lobectomy or pneumonectomy) adjuvant radiation therapy
stage 2b	tumor may be more than 3 cm, may have spread to the pleura, or partially blocks a bronchus and has spread to local lymph nodes alternately, tumor may be of any size and involves the chest wall, mainstem bronchus within 2cm of carina, or causes atelectasis of the whole lung	surgery (lobectomy or pneumonectomy) adjuvant radiation therapy possible adjuvant chemotherapy
stage 3a	tumor may be of any size and involves the chest wall, mainstem bronchus within 2cm of carina, or causes atelectasis of the whole lung extension to mediastinal lymph nodes	radiation therapy and CHEMOTHERAPY in combination possible surgery
stage 3b	tumor may be of any size but there is extensive, unresectable invasion of local structures and/or distant lymph node involvement	radiation therapy and chemotherapy in combination, possibly in preparation for surgery
stage 4	cancer has spread to locations distant from the lung	palliative chemotherapy or radiation therapy supportive care

STAGING OF SMALL CELL LUNG CANCER (SCLC)

Stage	Extent of Cancer	Treatment Protocols/Options
limited	cancer is present in only one lung though may have spread to adjacent LYMPH nodes	CHEMOTHERAPY, possibly in combination with RADIATION THERAPY possibly surgery if small, localized tumor without further involvement possible prophylactic cranial irradiation (PCI)
extensive	cancer is present in both LUNGS, adjacent lymph nodes, and other organs (disseminated disease)	chemotherapy palliative measures to relieve symptoms

The least aggressive of the three types of NSCLC is squamous cell carcinoma, which most commonly occurs as a consequence of cigarette smoking. Some people have more than one type of NSCLC at the time of diagnosis.

Small Cell Lung Cancer (SCLC)

Cigarette smoking causes nearly all SCLC. Small cell lung cancer has a characteristic appearance microscopically, sometimes described as "oat cell." This type of lung cancer grows rapidly and often has metastasized by the time of diagnosis. The outlook (prognosis) for extensive SCLC is particularly poor, with a one-year survival rate of about 20 percent. About 70 percent of people have extensive SCLC at the time of diagnosis.

Malignant Mesothelioma

Malignant mesothelioma is a rare form of cancer that occurs mostly in people who have had exposure to asbestos, particularly those who have ASBESTOSIS (a condition of damage to the lungs resulting from asbestos exposure). Malignant mesothelioma commonly arises from the PLEURA, the membrane that covers the lung. Other mesothelial membranes in the body include the PERICARDIUM, which surrounds the HEART, and the peritoneum, which lines the abdominal cavity. Malignant mesothelioma may also arise from these membranes, though that is less common. Malignant mesothelioma often does not show symptoms until it is well advanced, invading the lungs and adjacent organs or spreading through the LYMPH vessels to sites throughout the body. Doctors diagnose about 2,000 people with malignant mesothelioma each year in the United States and stage it similarly to NSCLC.

NONMALIGNANT MESOTHELIOMA

A noncancerous form of mesothelioma, benign fibrous mesothelioma, may grow from the PLEURA to reach considerable size, compressing inward on the lung or causing PLEURAL EFFUSION. Treatment is surgery to remove the tumor, which cures the condition. Benign fibrous mesothelioma does not spread and does not return after removal, though new tumors may develop in other mesothelial membranes.

Symptoms and Diagnostic Path

Early symptoms of lung cancer are often general and do not point specifically to a pulmonary condition. These early symptoms include

- fatigue
- HEADACHE
- loss of APPETITE and unintended weight loss
- dizziness, confusion, and memory disturbances
- JOINT aches and BONE PAIN
- FEVER without evidence of INFECTION

As the cancer becomes more established and takes over more of the lung, symptoms are more specific. These more specific symptoms include

- persistent COUGH
- HEMOPTYSIS (coughing up bloody sputum)
- chest or back pain
- wheezing (whistling sound with exhalation)
- DYSPNEA (shortness of breath)

The diagnostic path begins with a comprehensive medical examination including chest X-RAY and diagnostic blood tests. The chest X-ray may show an abnormality that, with an appropriate history, would suggest a diagnosis of cancer. Further diagnostic procedures may include COMPUTED TOMOGRAPHY (CT) SCAN, MAGNETIC RESONANCE IMAGING (MRI), POSITRON EMISSION TOMOGRAPHY (PET) SCAN, and lung biopsy, BRONCHOALVEOLAR LAVAGE, or exploratory THORACOTOMY.

A crucial element of diagnosis and treatment planning is staging, which identifies the extent to which the cancer has spread. Doctors may perform additional diagnostic procedures to determine the lung cancer's stage. Non–small cell lung cancer and malignant mesothelioma follow a standard cancer staging scale. Because SCLC is so extraordinarily aggressive it follows a unique staging scale that primarily defines the disease as either limited or extensive.

Treatment Options and Outlook

Treatment options and outlook vary according to the type and stage of lung cancer as well as the person's overall health status. Recommendations

regarding staging and treatment options are prone to change as more research and clinical trials are available. An important part of the approach to managing care is ensuring access to current treatment protocols that may include investigational regimens. Most treatment protocols combine different therapies for optimal effectiveness. Nutritional support during cancer treatment is important to help the body fight the cancer and heal. The available treatments for lung cancer include

- Surgery, which removes the cancerous tumor and portion of the lung that contains it, is the treatment of first choice for NSCLC that remains relatively confined. When the cancer has spread to several locations within the same lung, the surgeon may remove the entire lung (pneumonectomy). Surgery may also be appropriate for very early stage SCLC, though SCLC is rarely found when it remains in an operable stage. The key risks of surgery include bleeding, infection, and limited lung function due to removal of part of the lung. Before surgery the person undergoes evaluation to estimate the ability to function after removal (resection) of part or all of the diseased lung.
- CHEMOTHERAPY, which launches a widespread attack on cancer cells throughout the body, is usually a second-line treatment that follows surgery (except in SCLC, for which it is often the first-line treatment) and may be the primary treatment for cancers that are inoperable or have already metastasized beyond the lungs. Common side effects of chemotherapy include fatigue, MOUTH sores, temporary HAIR loss, and NAUSEA and VOMITING.
- RADIATION THERAPY targets inoperable tumors or follows surgery to eradicate any residual cancer cells after the surgeon has removed the cancer. Radiation therapy may be preventive, as in prophylactic cranial irradiation (PCI) which targets the BRAIN to lower the risk for malignant METASTASES that might form there (the brain is a common metastatic site for lung cancer). Radiation therapy also may be the first-line treatment for limited SCLC or reserved for palliative, directed therapy (such as to treat an obstruction that develops in the lung).
- Photodynamic therapy (PDT) is a technique in which the oncologist administers a light-sensitive DRUG that the cancer cells absorb and then targets the cells with a laser that generates light waves to activate the drug and kill the cells that contain it. PDT may be the primary treatment for small or inoperable tumors, particularly those located in the airways. PDT increases the SKIN's sensitivity to the sun or other sources of ultraviolet light.
- Investigational treatments are available through clinical trials. Oncologists and thoracic surgeons are aware of what trials are ongoing for certain types of cancer or patient profiles and can suggest those that are appropriate. As well the U.S. Institutes of Health's National Cancer Institute (NCI) maintains a current listing of cancer trials, accessible at the NCI's Web site (www.cancer.gov/clinicaltrials). Investigational treatments in the clinical trial stage have shown promise in research studies and are undergoing testing in people. It is essential to fully understand the potential benefits (personal as well as for the treatment of lung cancer in general) and risks of any investigational treatment when considering whether to participate in a clinical trial.

COMMON CHEMOTHERAPY DRUGS FOR TREATING LUNG CANCER

carboplatin	cisplatin	cyclophosphamide
dexamethasone	docetaxel	doxorubicin
etoposide	gemcitabine	ifosfamide
metoclopramide	paclitaxel	teniposide
topotecan	vincristine	vinorelbine

Risk Factors and Preventive Measures

Although not all lung cancer is associated with exposure to cigarette smoke, the vast majority is. In general, were it not for cigarette smoking lung cancer would be rare. This makes lung cancer one of the most preventable forms of cancer because eliminating exposure to cigarette smoke virtually eliminates the likelihood of developing lung cancer. People who smoke are at greatest risk, though people who live in households or work in environments where they continually breathe the smoke from cigarette smokers face nearly as great of a risk. Exposure to asbestos further compounds

the risk for cancer in people who smoke, making any type of lung cancer more likely as well as presenting the specific risk for malignant mesothelioma. The most effective measures for preventing lung cancer are not smoking and avoiding circumstances in which other people are smoking.

Exposure to radon, a naturally occurring gas that comes from the soil and can become concentrated within indoor areas such as homes and office buildings, is the second-leading cause of lung cancer. Radon is odorless and invisible, though radon detectors can measure its presence. The U.S. Environmental Protection Agency (EPA) has established a level of 4 picocuries per liter of air (4 pCi/L) as the maximum acceptable level. Simple ventilation measures can reduce or eliminate radon from indoor air.

See also ADENOMA-TO-CARCINOMA TRANSITION; CANCER PREVENTION; CANCER TREATMENT OPTIONS AND DECISIONS; ENVIRONMENTAL CIGARETTE SMOKE; PAIN MANAGEMENT IN CANCER; RADON EXPOSURE; SMOKING AND CARDIOVASCULAR DISEASE; SMOKING AND PULMONARY DISEASE.

lungs The paired organs in the chest that bring oxygen-bearing air into the body and expel wastes in the form of exhaled gases, primarily carbon dioxide. The right lung has three lobes and the left lung has two lobes. An indentation between the left lung's two lobes, called the cardiac notch, cradles the HEART. The lungs and heart, along with their supporting structures, fill the thoracic cavity (chest). The heart pumps deoxygenated BLOOD to the lungs via the PULMONARY ARTERIES and receives oxygenated blood back from the lungs via the PULMONARY VEINS, circulating the body's entire blood volume through the lungs once every minute.

The TRACHEA (windpipe) carries air from the THROAT into the lungs, branching into the right and left BRONCHUS to deliver air to the right and left lung, respectively. Each bronchus further subdivides into mainstem bronchi going to each lobe of the lung and into progressively smaller bronchial branches within the lungs. The smallest branches are the bronchioles which terminate in the alveoli, grapelike clusters of tiny sacs where the OXYGEN–CARBON DIOXIDE EXCHANGE takes place. A weblike mesh of capillaries (tiny blood vessels) covers each ALVEOLUS. Each lung contains about 300 million alveoli, which gives lung tissue a spongelike appearance.

Each lobe of the lung consists of multiple segments, anatomically and physiologically distinct. A bronchial structure—bronchi, bronchioles and alveoli along with supporting nerves, arteries, and veins—supplies each segment. The three lobes of the right lung contain 10 segments; the two lobes of the left lung contain 8 segments. This structural and functional compartmentalization aids the efficiency of the lung as well as helps protect it in the event of injury (either traumatic or due to disease), enabling portions of the lung to function when others are damaged or diseased.

Lung tissue contains elastin, a substance that, as the name implies, gives the lung tissue elasticity. The lungs have no ability to move on their own but rather function as a pair of synchronized bellows that stretch and rebound with contraction and relaxation of the DIAPHRAGM and the intercostal muscles (the muscles between the ribs). Contraction of these muscles expands the chest, and the lungs stretch to fill the space which pulls air into the lungs. When these muscles relax, the chest returns to its normal size and the lungs rebound, pushing air back out of the lungs. Each combination of inhalation and exhalation constitutes a RESPIRATORY CYCLE. The lungs complete 15 to 20 respiratory cycles each minute in a healthy adult.

HEALTH CONDITIONS THAT AFFECT THE LUNGS

ASBESTOSIS	ASPERGILLOSIS
ASTHMA	ATELECTASIS
BERYLLIOSIS	BRONCHIECTASIS
BRONCHITIS	BYSSINOSIS
CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)	CYSTIC FIBROSIS
LUNG ABSCESS	LEGIONNAIRES' DISEASE
PNEUMOCONIOSIS	LUNG CANCER
PNEUMONITIS	*Pneumocystis carinii*
PULMONARY EMBOLISM	PULMONARY EDEMA
PULMONARY HYPERTENSION	PULMONARY FIBROSIS
TUBERCULOSIS	SILICOSIS

Oxygen–carbon dioxide exchange, the process of getting oxygen into and removing carbon dioxide from the blood, is the primary purpose of the lungs and is a function of physics in which mole-

cules follow the path of least resistance. During inhalation the air pressure within the alveoli is less than the air pressure outside the lungs. Oxygen molecules pass across the thin alveolar membrane and into the capillaries to enter the bloodstream. During exhalation the air pressure within the alveoli is greater than the atmospheric air pressure, inducing carbon dioxide molecules to cross from the capillaries into the air in the alveoli.

For further discussion of the lungs within the context of pulmonary structure and function please see the overview section "The Pulmonary System."

See also EPIGLOTTIS.

lung transplantation An OPERATION to replace an individual's diseased lung with a healthy donor lung. Doctors performed the first successful lung transplantation in 1983 and now perform several hundred lung transplantations each year. A lung transplantation may involve one lung or both LUNGS. Less commonly a lung transplantation includes both lungs and the HEART, such as to treat primary PULMONARY HYPERTENSION with HEART FAILURE.

Donor lungs come primarily from people who donate their organs upon death. Live lobular donation, in which a living donor undergoes surgery to have a lobe of the lung removed for transplantation (lobectomy), is occasionally a viable option for people who can find a tissue match among two prospective donors (usually family members) willing and medically capable of donating a healthy lung lobe (live lobular donation typically requires two lobes). Doctors most commonly consider living lobular donation as an option for children who have aggressive CYSTIC FIBROSIS.

Many circumstances influence whether an individual is an appropriate candidate for lung transplantation. Because donor lungs are in short supply, the criteria for transplantation are stringent though vary somewhat among transplant centers. In general, lung transplantation recipients must be under age 65, in good health except for their pulmonary conditions, and demonstrate willingness and ability to comply with the post-transplantation care regimen. Transplantation criteria nearly always exclude people who have cancer (lung or other), immunodeficiency disorders, active TUBERCULOSIS, neurologic or neuromuscular disorders, LIVER disease, or renal (kidney) disease.

CONDITIONS FOR WHICH LUNG TRANSPLANTATION IS AN OPTION

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)	CYSTIC FIBROSIS
bronchiolitis	BRONCHIECTASIS
primaryPULMONARY HYPERTENSION	alpha-1-antitrypsin deficiency
PULMONARY FIBROSIS	SARCOIDOSIS

Surgical Procedure

The operation for performing a lung transplantation is a THORACOTOMY, done with the person under general ANESTHESIA. The surgery generally takes three to six hours to complete. Typically one surgical team removes and prepares the donor lung and another surgical team removes the diseased lung from the person receiving the lung transplantation. A donor lung remains viable for only four to six hours. Most people are on CARDIOPULMONARY BYPASS during the surgery, though advances in surgical techniques are reducing the need for this. MECHANICAL VENTILATION during recovery and for up to 72 hours after surgery is common. A lung transplant recipient typically stays about 10 days in the hospital after the surgery, the first three to five of them in the intensive care unit (ICU). Recuperation and return to daily activities takes about three to five months for most people.

Risks and Complications

The most significant risk of lung transplantation is rejection of the transplanted lung. This risk is highest during the first four weeks after the surgery and remains a perpetual threat. The risk of death, usually resulting from acute organ rejection, is highest during the first year after the transplant. People who receive organ transplants must take IMMUNOSUPPRESSIVE THERAPY for the remainder of their lives. These medications block the IMMUNE SYSTEM from perceiving the transplanted organ as foreign and attacking it. Immunosuppressive therapy increases the risk for INFECTION. Infections such as INFLUENZA or PNEUMONIA can be life-threatening for people with organ transplants; most transplant programs require organ recipients to agree to receive annual immunizations to help protect

against these infections among their criteria for accepting recipients. Long-term immunosuppression carries numerous risks, including a significantly increased likelihood for developing LYMPHOMA, a cancer of the LYMPH structures.

A major complication that affects up to 50 percent of lung transplant recipients is bronchiolitis obliterans, a condition in which the bronchioles (the smallest airways in the lungs) become inflamed and then fibrotic. The fibrotic (SCAR) tissue blocks the narrow openings of the bronchioles, preventing air from reaching the alveoli. As greater numbers of bronchioles become involved, pulmonary function deteriorates. Bronchiolitis is itself an indication for lung transplantation. CORTICOSTEROID MEDICATIONS can help limit the INFLAMMATION though cannot prevent the condition from developing or progressing.

Outlook and Lifestyle Modifications

Most people who receive transplanted lungs can return to many of their regular activities, including physical exercise, with few restrictions unless complications develop. It is important to avoid cigarette smoke and other substances that may irritate or inflame the lungs, and to minimize exposure to other people who have viral or bacterial infections such as sore throats and other common illnesses. Lung transplantation requires regular medical care for follow-up and evaluation of pulmonary function and lung health, with immediate treatment for potential problems and complications. About 45 percent of people who undergo lung transplantation live five years or longer with their donor lungs.

See also HEART TRANSPLANTATION; ORGAN TRANSPLANTATION; SURGERY BENEFIT AND RISK ASSESSMENT.

mechanical ventilation A method for providing assisted respiration to an individual whose LUNGS cannot maintain respiratory support on their own (RESPIRATORY FAILURE). During mechanical ventilation, a machine (the ventilator) rhythmically pushes air into the lungs through an endotracheal tube or TRACHEOSTOMY tube. An endotracheal tube is a flexible plastic tube inserted through the NOSE or MOUTH into the TRACHEA, with an inflatable cuff that holds it in place. A tracheostomy tube enters the trachea through an incision in the neck, bypassing the upper airways (including the mouth and throat). The lungs continue to do the work of OXYGEN–CARBON DIOXIDE EXCHANGE.

Mechanical ventilation may provide full respiratory support, in which BREATHING occurs only with the ventilator's function, or partial respiratory support, in which the ventilator functions only when the person's natural breathing is insufficient. As with normal respiration the inhalation phase of the RESPIRATORY CYCLE is active, with the ventilator sending air under pressure into the lungs, and the exhalation phase is passive, with the ventilator allowing the thoracic cavity's relaxation to expel air. The ventilator typically utilizes continuous POSITIVE AIRWAY PRESSURE (CPAP), which keeps the trachea, bronchi, and bronchioles from collapsing.

There are numerous applications for, and varying levels of, mechanical ventilation. Temporary mechanical ventilation is customary after major cardiovascular or pulmonary operations and during recovery from major trauma. Other circumstances in which mechanical ventilation is a therapeutic option include

- high-level (cervical and upper thoracic) SPINAL CORD INJURY that affects the nerves regulating contraction of the DIAPHRAGM and intercostal muscles (the muscles of breathing)
- injury to the respiratory centers of the BRAIN and brainstem
- degenerative neurologic conditions that affect respiratory function
- increased respiratory demands that exceed the lungs' ability to deliver, such as in severe infections

The ventilator is primarily a mechanized bellows that fills with air (and supplemental oxygen if necessary) that inflates the lungs using positive pressure. The doctor determines the RESPIRATORY RATE, air volume (amount of air the ventilator delivers), and flow pressure (pressure under which the ventilator delivers air to the person). In some situations the person does not need help with breathing but just needs an endotracheal tube or tracheostomy to protect the airway and minimize the risk of aspirating foreign matter into the lungs. In such a situa-

tion the tube may connect only to an oxygen source without a ventilator.

THE IRON LUNG

One of the first mechanical ventilators was nicknamed the iron lung. This device, which used a vacuum pump within a sealed chamber to cause the chest to rise, debuted during the POLIOMYELITIS epidemics of the 1930s and 1940s. Though cumbersome (it encased the person from toes to neck), the iron lung saved countless lives.

Complications of short-term mechanical ventilation are usually minor and may include sore throat (from the endotracheal tube) and INFECTION. Infection is a greater risk with long-term mechanical ventilation, with PNEUMONIA being the most common. The longer a person receives mechanical ventilation, the more difficult it becomes to wean the person to breathe independently. Long-term mechanical ventilation becomes an element of life support, which raises questions of QUALITY OF LIFE. Doctors encourage adults to establish advance directives to help guide life-support decisions.

See also ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS); CARDIOPULMONARY BYPASS; OXYGEN SATURATION.

middle lobe syndrome See ATELECTASIS.

oxygen–carbon dioxide exchange The process by which oxygen passes from the air in the LUNGS to the HEMOGLOBIN in the BLOOD, and carbon dioxide from the hemoglobin passes into the air in the lungs. Oxygen–carbon dioxide exchange is fundamental to life and is the primary function of the lungs. Oxygen–carbon dioxide exchange takes place between the alveoli, the tiny bubblelike sacs deep within the lungs, and the capillaries, the tiniest blood vessels of the cardiovascular system. The membranous tissue of an ALVEOLUS is only one cell or two cells in thickness. A mesh of capillaries encloses each of the 300 million or so alveoli in the lungs. The walls of the capillaries are also only one cell in thickness. Some disease states cause this interface to thicken, thus making the oxygen–carbon dioxide exchange ineffective.

Oxygen and carbon dioxide molecules (as well as the molecules of other gases such as nitrogen and highly toxic carbon monoxide) can easily pass through the walls of the alveoli and the capillaries, moving in the direction of least resistance. Oxygen molecules move from the alveoli into the capillaries with inhalation. Hemoglobin molecules in the erythrocytes (red blood cells) attract the oxygen molecules, binding with them to carry them through the bloodstream. At exhalation carbon dioxide molecules cross the alveolar membrane to join the gases within the alveoli. Exhalation expels the carbon dioxide into the atmosphere.

Factors that influence oxygen–carbon dioxide exchange include the concentration of oxygen in the air, which is about 21 percent at sea level and decreases with elevation.

Numerous pulmonary conditions affect oxygen–carbon dioxide exchange. Infections such as INFLUENZA and PNEUMONIA can cause the alveoli to fill with fluid, blocking air from reaching the alveolar membranes. Inhaled substances, notably cigarette smoke, can clog small bronchioles, preventing air from reaching the alveoli. Eliminating their causes usually reverses most if not all of these circumstances to restore full function (though damage resulting from long-term cigarette smoking or repeated pneumonia can become permanent). Conditions that cause scarring (fibrosis), such as CYSTIC FIBROSIS, SARCOIDOSIS, PNEUMOCONIOSIS, and untreated TUBERCULOSIS, block air from reaching the alveoli. ATELECTASIS and BRONCHIECTASIS are collapses of lung segments that also block the movement of air into the deep lung tissues. Conditions in which the alveoli rupture and form enlarged sacs, such as alpha-1-antitrypsin deficiency (an inherited genetic disorder), destroy the surface area and reduce the effectiveness of the gas exchange. Both late-stage CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) and early emphysema-predominant COPD cause scarring and alveolar rupture. Such structural damage is permanent.

See also CYSTIC FIBROSIS AND THE LUNGS; LUNG TRANSPLANTATION; OXYGEN SATURATION; OXYGEN THERAPY.

oxygen saturation The percentage of HEMOGLOBIN molecules in the BLOOD that are bound to oxygen molecules. Normal oxygen saturation of the arterial blood is 96 to 98 percent. Saturation significantly below normal, for instance 88 percent, indicates RESPIRATORY FAILURE and may be life-threatening. Oxygen saturation is an essential measurement for assessing cardiovascular and pulmonary effectiveness. Inadequate oxygen saturation in the blood is hypoxemia.

The primary method for measuring oxygen saturation is pulse oximetry, which is painless and noninvasive. The pulse oximeter consists of two

components, an emitter and a tiny computer chip. The emitter is a small device that fits over the fingertip or on the EAR lobe. It projects beams of red and infrared light, which pass through the tissue to a sensor on the other side. The volume of blood in the tissue at systole (peak contraction of the HEART) is greater, resulting in more light being absorbed than with the lesser volume of blood in the tissue at diastole (relaxation of the heart). The oximeter's computer chip measures this difference and uses it to mathematically calculate the percentage of oxygen the hemoglobin carries.

See also OXYGEN–CARBON DIOXIDE EXCHANGE; OXYGEN THERAPY.

oxygen therapy The administration of oxygen via nasal cannula, face mask, endotracheal tube (tube inserted into the THROAT), or transtracheal catheter (small tube surgically placed through the outside of the throat into the TRACHEA). Oxygen therapy delivers oxygen at a percentage higher than that of normal air, which is 21 percent oxygen at sea level. Oxygen therapy can deliver oxygen from about 25 percent to 100 percent. This boosts the OXYGEN SATURATION of the BLOOD, which becomes necessary when the LUNGS cannot adequately diffuse oxygen into the blood or the HEART cannot circulate oxygenated blood at a level that meets the body's needs.

Oxygen is highly flammable. Do not smoke, have an open flame, or use electrical appliances (including extension cords) in the vicinity of the oxygen supply.

Because 100 percent oxygen can be harmful to body tissues, doctors administer this level of oxygen therapy only to treat respiratory crisis. Supplemental oxygen therapy may be an element of treatment for cardiovascular conditions such as ISCHEMIC HEART DISEASE (IHD) and HEART FAILURE as well as pulmonary conditions such as CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD), PNEUMONIA, severe ASTHMA, and ATELECTASIS.

In the hospital setting the oxygen supply is centralized, with access ports in patient care areas. Oxygen-delivery tubing plugs into the port, with an individualized flow regulator to adjust the percentage of oxygen. Oxygen tanks for home oxygen therapy contain compressed or frozen (liquid) oxygen, with flow regulators and often a device that releases oxygen only on inhalation. Home oxygen therapy may use an oxygen concentrator instead of supplemental oxygen. An oxygen concentrator extracts nitrogen from room air to increase the air's concentration of oxygen. Oxygen concentrators can deliver oxygen only at low flow rates, however, making them useful only for people who require minimal oxygen supplementation. It is important to have adequate supplemental humidification as well during oxygen therapy, as the higher concentration of oxygen is drier than environmental air. Oxygen therapy may be short-term or long-term treatment, depending on the condition that causes its use. The person may also use oxygen therapy continuously, only during sleep, or only during physical activity depending on his or her underlying disease and respiratory needs.

OXYGEN THERAPY

Oxygen Therapy Device	Percentage of Oxygen
nasal cannula	25 to 40 percent
face mask	30 to 50 percent
nonrebreathing mask	50 to 90 percent
transtracheal catheter	up to 100 percent
endotracheal tube	up to 100 percent
bag and mask resuscitator	up to 100 percent

See also OXYGEN–CARBON DIOXIDE EXCHANGE; TRACHEOSTOMY.

P

pleura The membrane that covers the exterior surface of the LUNGS and lines the inside of the thoracic cavity. The pleura has the consistency of wet tissue paper and appears to cling to the lungs. The pleural space (thin area between the two layers of pleura) protects the lungs from contact with other structures within the thoracic cavity, and contains a very small amount of fluid that reduces friction with BREATHING. The pleural space can become irritated, inflamed, and infected, causing conditions such as PLEURISY and PLEURAL EFFUSION.

For further discussion of the pleura within the context of pulmonary structure and function please see the overview section "The Pulmonary System."

See also ALVEOLI; BRONCHUS; INFECTION; INFLAMMATION; THORACIC DUCT; TRACHEA.

pleural effusion An increase in the amount of fluid between the PLEURA. In health there is a very small amount of fluid, only 10 to 20 milliliters, within the pleural cavity. A pleural effusion can contain upward of 2 liters of fluid, though much smaller quantities (less than 400 milliliters) are more common. Pleural effusion compresses the LUNGS, preventing them from fully expanding. Many conditions can cause pleural effusion. Pleural effusion is exudative when it results from INFLAMMATION of the pleura (PLEURISY). Pleural effusion is transudative when pressure changes in the body's fluid balance (osmotic) mechanisms allow more fluid to cross the pleural membrane such as with HEART FAILURE. A hemothorax exists when the excess fluid is BLOOD, and a chylothorax occurs when the excess fluid is LYMPH.

Many people who have pleural effusion have no symptoms. When present, symptoms include

- DYSPNEA (shortness of breath or difficulty BREATHING)
- CHEST PAIN, primarily with inhalation
- fatigue or weakness

The diagnostic path typically includes chest X-RAY, COMPUTED TOMOGRAPHY (CT) SCAN or ULTRASOUND, and THORACENTESIS (withdrawing a sample of the fluid using a syringe with a large needle). Treatment aims to reduce the volume of fluid as well as identify the underlying cause (such as infection). Thoracentesis may also be therapeutic, allowing the pulmonologist to drain away the excess fluid. Doctors generally drain no more than 1.5 liters of fluid at a time because more substantial withdrawal can result in rapid fluid shifts, causing cardiovascular instability and the development of pulmonary edema (fluid accumulation in the lung tissue). Recovery depends on the condition causing the pleural effusion.

See also LUNG CANCER; PULMONARY EDEMA.

pleurisy INFLAMMATION of the PLEURA, also called pleuritis. Pleurisy can develop as a consequence of direct irritation or INFECTION in the pleural space, or as a consequence of infection or INFLAMMATION involving the LUNGS such as TUBERCULOSIS or PNEUMONIA. AUTOIMMUNE DISORDERS can cause inflammation, such as SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) and SARCOIDOSIS. The characteristic symptom of pleurisy is sudden, sharp, and often severe PAIN during inhalation and exhalation that subsides with holding the breath. The pain may occur on only one side of the chest or both sides, and may feel as though it comes from the back or under the shoulder blades, depending on the site of the inflammation. Some people also have a persistent, dry COUGH.

Upon AUSCULTATION with a STETHOSCOPE the doctor can hear an abnormal abrasive sound called a pleural rub, which is the sound of the irritated layers of the pleura rubbing against each other. Chest X-RAY confirms whether there is PLEURAL EFFUSION in which the pleural cavity contains excessive fluid. The doctor may also choose to do an ULTRASOUND or COMPUTED TOMOGRAPHY (CT) SCAN of the thorax.

Treatment targets any underlying cause, when identified. For simple pleurisy, treatment is usually NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) to relieve inflammation and pain. The doctor may also prescribe a cough medicine to control coughing. Most people cover fully and uneventfully from an episode of pleurisy. People who have chronic pulmonary conditions or who smoke may have recurrent pleurisy, which can result in long-term thickening or scarring of the pleura.

See also BRONCHITIS; PERICARDITIS; PNEUMONITIS; SMOKING AND HEALTH.

pneumoconiosis The collective term for pulmonary conditions that result from occupational exposure to dust and fiber irritants. The conditions result in the same end-stage disease, pulmonary fibrosis, though follow different patterns of progression, depending on the substance and exposure patterns. The primary forms of pneumoconiosis that occur in the United States are

- ANTHRACOSIS, also called coal worker's pneumoconiosis (CWP) and black lung disease, which results from inhalation of coal dust
- ASBESTOSIS, which results from inhalation of asbestos fibers and dust
- BERYLLIOSIS, which results from inhalation of beryllium dust
- BYSSINOSIS, also called brown lung and cotton bract disease, which results from inhalation of raw cotton fibers and dust
- SILICOSIS, which results from inhalation of silica dust

U.S. occupational health experts and federal agencies began tracking and reporting deaths due to pneumoconiosis in 1968, as data related to occupational health. The federal Coal Mine Health and Safety Act of 1969, which established levels of dust exposure standards, was the first substantial effort in the United States to reduce such deaths. The Black Lung Act of 1972 further acknowledged the significant occupational health problems of coal workers, expanding the regulatory scope of the 1969 legislation and establishing a program of government-funded health care for coal workers who developed anthracosis (called black lung disease in the legislation and regulations).

Federal regulation controls occupational exposure to other sources of pneumoconiosis, notably silica, as well. Health experts attribute the declining numbers of diagnoses and deaths in all pneumoconioses, except asbestosis, largely to such controls. The number of people diagnosed with and who die from asbestosis continues to climb, however, because the time between exposure and illness is a minimum of 20 years. Regulatory changes will benefit workers who began working in affected occupations in the last decades of the 20th century, though health experts anticipate that asbestosis will keep rising among those whose work history predates regulations as their average age increases. Peak exposure to asbestos in the United States occurred in 1975, according to the U.S. Centers for Disease Control and Prevention (CDC), so health experts expect asbestos-exposure related illness to peak between 2015 and 2020. However, asbestos exposure in general dropped significantly after the late 1970s when federal legislation restricted the use of asbestos in materials such as building insulation, ceiling tiles, and flooring.

The other key factor contributing to diminishing disease and death rates for pneumoconiosis is the declining numbers of people working in occupations where exposure is a hazard. The number of coal miners in the United States dropped by half between the 1980s and the 1990s, for example, as more mining functions have become automated or mechanized. Automation continues to reduce hazardous occupational exposures in most industries.

Symptoms and Diagnostic Path

Dry, nonproductive COUGH and DYSPNEA (shortness of breath), particularly with exertion, are the key symptoms of most forms of pneumoconiosis. Anthracosis, berylliosis, byssinosis, and silicosis

FORMS OF PNEUMOCONIOSIS

Form of Pneumoconiosis	Causative Substance	Occupational Exposure
anthracosis	coal dust	coal mining
asbestosis	asbestos fibers and dust	insulation, aerospace components, brake lining, shipbuilding
berylliosis	beryllium dust	electronics, aerospace manufacturing, metal working, metal reclamation processing
byssinosis	raw cotton fibers and dust	raw cotton processing, textile production
silicosis	silica dust	sandblasting, sand and gravel mining

may show symptoms after relatively short periods of exposure and often improves when exposure ceases. Asbestosis may develop after relatively short exposure though symptoms typically do not become apparent for decades after exposure. The diagnostic path focuses on occupational history and exposure patterns. Diagnostic examination typically includes AUSCULTATION, chest X-RAY, pulmonary function tests, and imaging procedures such as ULTRASOUND, COMPUTED TOMOGRAPHY (CT) SCAN, or MAGNETIC RESONANCE IMAGING (MRI). The pulmonologist may also perform BRONCHOSCOPY, BRONCHOALVEOLAR LAVAGE, or lung biopsy to rule out other causes of symptoms.

Treatment Options and Outlook

The first and most important element of treatment is to end the exposure. Nearly all forms of pneumoconiosis improve with this measure. Permanent damage to the lungs that has already occurred, such as fibrosis, does not reverse though its progression may stop. The disease process of asbestosis is such that damage continues long after exposure ceases. The outlook depends on the form of pneumoconiosis, the length or extent of exposure, and whether the person also smokes. Cigarette smoking significantly worsens both the disease process and the outlook.

Risk Factors and Preventive Measures

Occupational pneumoconiosis develops with exposure to substances that enter and remain in the lungs. Avoiding such exposure is the only certain means of prevention. Workplace measures to reduce exposure to the lowest possible levels include environmental controls to filter or otherwise contain dusts and fibers. Personal protective equipment may include clothing, masks, and respirators.

See also ASTHMA; BRONCHITIS; CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD); INDOOR AIR QUALITY; OCCUPATIONAL HEALTH AND SAFETY.

pneumonectomy See THORACOTOMY.

pneumonia INFLAMMATION of the LUNGS, usually the result of an INFECTION, that causes the alveolar sacs to fill with fluid or pus. Pneumonia is the most serious consequence of INFLUENZA, and in combination with influenza is the seventh leading cause of death in the United States. Pneumonia may be lobar, affecting the entire lobe of the lung, or bronchial, affecting diffuse areas of lung. The more of the lung that is involved, the more serious the consequences. People most vulnerable to infection resulting in pneumonia and complications from pneumonia are the very young, the very old, and those who have immunodeficiency disorders such as HIV/AIDS or other serious health conditions such as CANCER. About two million people in the United States develop pneumonia each year, and about 60,000 die as a result of the infection or its complications.

Pathogens that can cause pneumonia include viruses, BACTERIA, and fungi. The pneumonias that result from these pathogens are contagious—that is, an infected person can pass them to others through sneezing and coughing. SPUTUM (mucus and debris from the respiratory tract) contains the infective agent. Pneumonia also can develop after exposure to bacteria aspirated into the lungs (such as in a person who is weak and vomiting). Nosocomial pneumonias develop from pathogens common in environments such as hospitals and skilled nursing facilities and infect people who are already weak as a result of other health conditions (especially those who are IMMUNOCOMPROMISED).

Viral Pneumonia

A number of viruses can cause pneumonia, the most common of which are influenza A, influenza B, parainfluenza, respiratory syncytial VIRUS, ADENOVIRUS, varicella-zoster virus, EPSTEIN-BARR VIRUS, and coxsackievirus. CYTOMEGALOVIRUS (CMV) pneumonia can develop in people who are IMMUNOCOMPROMISED. ANTIVIRAL MEDICATIONS are available for some of these viral infections and can shorten the course of the infection and lessen the severity of symptoms. Most otherwise healthy people recover fully from viral pneumonia. Bacterial pneumonia may develop secondarily to viral pneumonia.

Bacterial Pneumonia

Pneumonia in people over age 30 is more likely to result from bacterial infection than other causes. *Staphylococcus aureus, Haemophilus influenzae* type b (Hib), *Chlamydia pneumoniae,* and *Streptococcus pneumoniae* are the strains of bacteria most commonly responsible for bacterial pneumonia. *S. pneumoniae* causes the most common form of bacterial pneumonia, pneumococcal pneumonia, which often follows a viral infection of the upper respiratory tract. Hib pneumonia, despite the bacterium's name, has nothing to do with the influenza virus and affects primarily young children. Hib vaccination has nearly eliminated this type of pneumonia among children in the United States. *S. aureus* tends to be opportunistic and accounts for about 20 percent of nosocomial pneumonia. ANTIBIOTIC MEDICATIONS are necessary to treat bacterial pneumonia. Even with antibiotic therapy, however, bacterial pneumonia is a serious illness that can be deadly among the very young and the very old.

Mycoplasmal Pneumonia

Mycoplasma are tiny organisms related to bacteria, commonly called atypical bacteria. The pneumonia they cause is typically mild though tends to linger. A common nickname for mycoplasmal pneumonia as "walking pneumonia" because its symptoms are enough to make people feel unwell though usually not enough to interrupt regular activities. Most people recover without treatment, though antibiotics usually speed recovery. COUGH and HEADACHE may persist for several weeks.

Fungal Pneumonia

Fungi may cause pneumonia in people who take antibiotics for an extended period of time, as antibiotics suppress the NORMAL FLORA (normally present bacteria) that otherwise keep fungi in check. Fungal pneumonias are rare but when invasive in someone who is immunocompromised, they can be life-threatening.

Pneumocystic Carinii Pneumonia

Pneumocystis carinii is an opportunistic pneumonia that occurs nearly exclusively in people who are immunocompromised, including those who have HIV/AIDS, are receiving IMMUNOSUPPRESSIVE THERAPY following organ transplantation, or are undergoing chemotherapy for cancer treatment. During the early days of the AIDS epidemic, *P. carinii* pneumonia was often the first indication that a person had HIV/AIDS. Doctors may prescribe prophylactic ANTIFUNGAL MEDICATIONS for people at risk for *P. carinii* pneumonia. Such prophylaxis has now made *Pneumocystic* pneumonia a relatively rare event in people whose HIV infection is well-managed.

Symptoms and Diagnostic Path

The symptoms of pneumonia vary somewhat with the type of pneumonia, though commonly include

- cough that produces greenish yellow sputum or HEMOPTYSIS (bloody sputum)
- FEVER (sometimes high)
- chills or sweating

- generalized discomfort and aches
- fatigue
- chest discomfort or PAIN, especially with inhalation
- DYSPNEA (shortness of breath) or TACHYPNEA (rapid BREATHING)

Symptoms may develop gradually or come on suddenly. Though the pattern of the symptoms provides good clues as to the cause of the pneumonia, the doctor cannot determine whether the infection is viral or bacterial without sputum or blood tests. Viral pneumonia does not respond to antibiotic therapy, though a good number of people who have viral pneumonia develop secondary bacterial pneumonia that does require antibiotics. The diagnostic path typically includes chest X-ray, which shows the areas of infiltration (fluid or pus accumulation) within the lungs. Other factors that help determine the kind of pneumonia include knowledge of local or regional outbreaks of viral or bacterial pneumonia, history of recent upper respiratory infection or influenza, and the presence of other health conditions such as HIV/AIDS. Sputum culture may also help in the diagnosis although most viruses and atypical bacteria do not readily grow in culture.

Treatment Options and Outlook

Treatment depends on the cause of the infection and may include antibiotics for bacterial pneumonia, antiviral medications or management of symptoms for viral pneumonia, and antifungal medications for fungal pneumonia. Because secondary bacterial pneumonia can develop as a complication of other types of bacteria, symptoms that fail to improve within 10 days or that worsen require further medical evaluation. Most people who are otherwise healthy make full recovery from pneumonia, though may take six to eight weeks to feel back to normal.

Risk Factors and Preventive Measures

The very young, the very old, and those who have serious health conditions of any kind are at greatest risk for pneumonia. Health experts recommend annual influenza IMMUNIZATION and pneumococcal vaccination for people who have such risks. Diligent HAND WASHING and conscientious cough and SNEEZE precautions help reduce the spread of infectious agents. Early diagnosis and appropriate treatment reduce the likelihood of complications.

See also ASPERGILLOSIS; CHEST PAIN; LEGIONNAIRES' DISEASE; NOSOCOMIAL INFECTIONS.

pneumonitis INFLAMMATION of the LUNGS resulting from exposure to an irritant. The inflammation causes the airways to narrow and to increase mucus secretion, reducing the pathways for the flow of air. The major types of pneumonitis are

- aspiration pneumonitis, which develops when foreign matter, such as vomitus or water, enters the airways and lungs
- chemical pneumonitis, which results from inhaling toxic fumes
- hypersensitivity pneumonitis, which is an IMMUNE REACTION to an inhaled substance
- radiation pneumonitis, which occurs as a SIDE EFFECT of RADIATION THERAPY to the chest and lower neck, such as to treat LUNG CANCER, THYROID CANCER, or BREAST CANCER

The primary symptoms of pneumonitis are persistent COUGH and DYSPNEA (shortness of breath). The doctor makes the diagnosis on the basis of the history of the symptoms, including when they began, what circumstances existed, and in particular any known or suspected exposures that occurred. Near drowning, for example, may result in aspiration of water. SWALLOWING DISORDERS may allow food or drink to enter the airways. Chemical pneumonitis and hypersensitivity pneumonitis often result from occupational exposures (and sometimes exposure to pets such as birds) and may indicate the early stages of pulmonary disease related to exposures such as to dusts and fibers. Chest X-ray, arterial BLOOD gases, pulmonary function tests, and chest computed tomography (chest CT) are among the diagnostic procedures that may help identify the extent of pulmonary involvement and its effect on oxygenation.

Treatment is often CORTICOSTEROID MEDICATIONS to relieve inflammation, which may allow the lungs to return to normal function. The doctor may also prescribe ANTIBIOTIC MEDICATIONS to treat

secondary INFECTION if present, or when the cause of the pneumonitis is bacterial infection. Elimination of irritants, when known, prevents the pneumonitis from recurring. Most people recover fully and without complications after the inflammation subsides. Chronic pneumonitis may result in scarring (fibrosis) and permanent damage to pulmonary structures, however.

See also ASTHMA; HYPOXIA; MULTIPLE CHEMICAL SENSITIVITY SYNDROME; PLEURISY; PNEUMOCONIOSIS; PNEUMONIA.

pneumothorax A circumstance in which air gets in the pleural space (membrane space between the pleural linings of the lung and the thoracic cavity). Pneumothorax results in collapse of a portion of, or the entire, lung. Doctors identify different kinds of pneumothorax. They include

- spontaneous pneumothorax, in which the pneumothorax occurs for no identifiable reason or as a consequence of severe lung disease such as CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) or TUBERCULOSIS
- simple pneumothorax, in which air enters the pleural space and part of all of the lung collapses but there is no pressure on surrounding structures
- tension pneumothorax, in which the pneumothorax occurs and pressure continues to build in the pleural space, putting pressure on the heart and causing potentially life-threatening cardiovascular collapse
- traumatic pneumothorax, in which air enters the pleural cavity as a result of injury or surgery

Symptoms include DYSPNEA (shortness of breath) and sudden, sharp PAIN that worsens with deep BREATHING or coughing. Some people develop CYANOSIS (bluish hue to the lips and SKIN) that indicates the body is not receiving enough oxygen. TACHYCARDIA (rapid HEART RATE), TACHYPNEA (rapid breathing), and HYPOTENSION (low BLOOD PRESSURE) are also common. The diagnostic path includes AUSCULTATION, which often reveals reduced or absent BREATH SOUNDS, and chest X-RAY, which shows the area of lung collapse.

A pneumothorax that involves only a small portion of the lung often heals itself. A larger pneumothorax requires insertion of a chest tube (done with local ANESTHESIA) to remove the air and allow the lung to reinflate. Most people who require such treatment stay in the hospital until the affected lung returns to normal function and the doctor can safely remove the chest tube. About half of people who have one episode of spontaneous pneumothorax have a subsequent episode, though most people do not experience any permanent lung damage. People who are tall and thin are most vulnerable to spontaneous pneumothorax. Spontaneous pneumothorax is also more common among people who smoke.

See also BRONCHIECTASIS.

positive airway pressure Methods to maintain higher than normal air pressure against the inner walls of the bronchi and TRACHEA during BREATHING. Positive airway pressure may be a treatment for ATELECTASIS (collapsed lung), chronic RESPIRATORY FAILURE, and SLEEP APNEA. Positive airway pressure is also an important aspect of MECHANICAL VENTILATION.

The most common method of positive airway pressure is continuous positive airway pressure (CPAP), in which a small pump pushes a steady flow of air through a face mask to maintain enough pressure against the airways to keep them open and unobstructed during sleep. CPAP is a common and an effective treatment for sleep apnea. Bilevel positive airway pressure, or BiPAP, is a flexible variation of CPAP. The conventional CPAP device maintains a constant airway pressure for inhalation and exhalation. BiPAP provides additional pressure or support during inspiration to aid inhalation.

See also BRONCHUS; OXYGEN THERAPY; SLEEP APNEA.

postural drainage See CHEST PERCUSSION AND POSTURAL DRAINAGE.

pulmonary edema Abnormal fluid accumulation within the alveoli and the interstitial tissues of the LUNGS, typically resulting from CARDIOVASCULAR DISEASE (CVD) such as HEART FAILURE or CARDIOMYOPATHY. PNEUMONIA, ACUTE RESPIRATORY DISTRESS SYNDROME

(ARDS), smoke inhalation, near drowning, and high altitude can also cause pulmonary edema.

Pulmonary edema can be a life-threatening condition and requires immediate medical evaluation and treatment.

The accumulated fluid of pulmonary edema limits air from entering the alveoli, affecting the OXYGEN–CARBON DIOXIDE EXCHANGE. The consequence is inadequate oxygen diffusion into the BLOOD with resulting HYPOXIA.

Symptoms and Diagnostic Path

The symptoms of pulmonary edema tend to come on quickly and include

- DYSPNEA (difficulty BREATHING), often severe or worse when lying down
- frothy HEMOPTYSIS (coughing up bloody SPUTUM)
- diaphoresis (profuse sweating or chills with sweating)
- HEADACHE or light-headedness
- COUGH
- Wheezing or gurgling sounds when breathing

Respiratory failure can rapidly develop. The diagnostic path includes AUSCULTATION with a stethoscope to listen to BREATH SOUNDS, which typically reveals rales (crackles). A chest X-RAY shows the accumulated fluid. Arterial blood gases assess the extent of hypoxia. Diagnostic procedures to evaluate cardiovascular function include ELECTROCARDIOGRAM (ECG), ECHOCARDIOGRAM, and CARDIAC CATHETERIZATION if the doctor suspects CORONARY ARTERY DISEASE (CAD) or MYOCARDIAL INFARCTION.

Treatment Options and Outlook

Treatment begins with OXYGEN THERAPY to improve oxygenation and, if the edema is from heart failure, usually diuretic medications to help pull the excessive fluid into the circulation so the KIDNEYS can pass it from the body. Additional treatment targets the underlying cause of the pulmonary edema, which may be cardiovascular or pulmonary. High altitude pulmonary edema (HAPE) requires prompt oxygen therapy with descent to a lower altitude as soon as is feasible. Climbers sometimes underestimate the seriousness of HAPE until symptoms become overwhelming and life-threatening. Any climber, regardless of high-altitude acclimation and climbing experience, is vulnerable to HAPE and all climbers should be familiar with early symptoms.

Pulmonary edema is a serious circumstance that can result in death when not promptly recognized and treated. The underlying cause determines the outcome. When the cause is cardiovascular, treatment may include CORONARY ARTERY BYPASS GRAFT (CABG) or ANGIOPLASTY to improve the flow of blood to the HEART. Medications may strengthen the heart and stabilize HEART RATE in heart failure, improving the heart's ability to pump blood. With appropriate treatment, many people recover completely from pulmonary edema. When the cause is noncardiogenic, such as due to severe infection or ARDS, treatment targets reversing the underlying disease and providing respiratory support until lung function returns to normal.

Risk Factors and Preventive Measures

The primary risk factor for cardiogenic pulmonary edema is cardiovascular disease. The most effective preventive measures are those that reduce the risks for cardiovascular disease: No smoking, maintain appropriate weight, exercise daily, and eat nutritiously. It is also important to take medications for diagnosed conditions such as HYPERTENSION (high BLOOD PRESSURE) as prescribed.

See also ASCITES; ESOPHAGEAL VARICES; PULMONARY HYPERTENSION.

pulmonary embolism A BLOOD clot that blocks the flow of blood through the main pulmonary ARTERY, the right or left pulmonary artery, or branching arteries within the lobes and segments of the LUNGS. Untreated pulmonary embolism can cause respiratory distress or death; about 30,000 people die each year in the United States as a result of pulmonary embolism.

Pulmonary embolism is a life-threatening condition that requires emergency medical care.

Pulmonary embolism is a potential complication of blood clots that develop within the veins,

typically the deep veins of the legs. It most commonly develops as a consequence of venous stasis, in which the blood moves sluggishly through the veins. The blood's slow movement allows blood to pool, permitting clots to begin to form especially on and around the valves in the veins. Clot fragments or the entire clot can break free, floating through the bloodstream.

Because the veins become larger as they approach the HEART, the bloodstream easily carries the clots through the right heart and into the pulmonary arteries and the lungs. Occasionally the clot that causes a pulmonary embolism originates in the heart's right atrium. Large clots can occlude (block) the pulmonary arteries at the point where the right and left pulmonary arteries diverge (bifurcation of the pulmonary artery).

As a consequence of the intimate correlation between alveolar function and the flow of blood through the capillary network that enmeshes the alveoli, the loss of capillary flow resulting from pulmonary embolism effectively shuts down all alveoli beyond (distal to) the site of the occlusion. Any loss of functioning alveoli subsequently limits the ability of the lungs to convey oxygen to the blood. The larger the occluded artery, the more immediate and significant the pulmonary consequences.

Symptoms and Diagnostic Path

The symptoms of pulmonary embolism vary widely and can be subtle or may be as severe and immediate as those of HEART ATTACK, and are similar. Such symptoms include

- sudden, severe CHEST PAIN
- DYSPNEA (difficulty BREATHING)
- diaphoresis (breaking into a cold sweat)
- HYPOTENSION (low BLOOD PRESSURE)
- TACHYCARDIA (rapid heart rate)
- TACHYPNEA (rapid BREATHING)

A person who experiences a massive pulmonary embolism may have little time between feeling fine and going into shock and cardiovascular collapse. Smaller emboli or recurrent (chronic) pulmonary embolism episodes generally produce milder variations of these same symptoms along with productive COUGH and HEMOPTYSIS (blood in the SPUTUM).

The diagnostic path seeks immediately to determine whether the symptoms are cardiovascular (heart attack) or pulmonary. An ELECTROCARDIOGRAM (ECG) does not show evidence of acute cardiac injury in pulmonary embolism, which is the first major point of differentiation. Arterial blood gases show how severely the pulmonary embolism is affecting the body's oxygenation. Diagnostic imaging procedures the pulmonologist may conduct include COMPUTED TOMOGRAPHY (CT) SCAN, MAGNETIC RESONANCE IMAGING (MRI), pulmonary angiography, and a specialized imaging procedure called ventilation/perfusion scan.

Treatment Options and Outlook

Hospitalization with intensive pulmonary support and immediate ANTICOAGULATION THERAPY is necessary for most circumstances of pulmonary embolism. The risk of death is highest within the first few hours of the embolism. Anticoagulation therapy targets preventing the formation of additional emboli. THROMBOLYTIC THERAPY ("clot buster" drugs) to dissolve the clots that have already formed is appropriate for some people. Surgery (either OPEN SURGERY or via catheterization) to mechanically break up the clot may be an option in severe situations. Recovery depends on the extent of lung affected, the existence of any underlying causes or health conditions, and the rapidity of diagnosis and treatment. People who recover from pulmonary embolism often require ongoing anticoagulation therapy though do not have significant permanent lung damage.

Risk Factors and Preventive Measures

Pulmonary embolism is most likely to occur in people who have restricted venous flow due to lower extremity VARICOSE VEINS or incompetent veins (veins that have lost elasticity and valve function), who are physically inactive, or who have recently had surgery or a major trauma (which means the body is forming clots for HEALING and also usually means limited physical movement). People who have untreated ATRIAL FIBRILLATION have increased risk for pulmonary embolism. OBESITY also increases the risk for pulmonary embolism because it exerts additional

resistance against the blood flowing through the veins. People who have an increased tendency to form clots (hypercoagulation) are also at increased risk of developing a clot or pulmonary embolism. Research suggests that as many as 80 percent of people who have DEEP VEIN THROMBOSIS (DVT) experience frequent pulmonary emboli. About half of the people who have one pulmonary embolism experience subsequent episodes.

Prevention often incorporates ongoing ANTICOAGULATION THERAPY in people at risk for pulmonary embolism, including those who have had a previous episode. Support stockings help the leg muscles to work more efficiently in massaging blood through the veins. For someone who has never had a pulmonary embolism, regular physical activity and maintaining healthy body weight help to lower the risk for clot formation. Frequent stretching of the legs, and getting up to walk for a few minutes every hour, can maintain effective circulation and venous return when taking long air flights or train or automobile trips to lower the risk for both DVT and pulmonary embolism. Postoperative recovery and recuperation regimens incorporate early ambulation (walking within hours of surgery) as well as progressive ambulation (walking for longer times and distances as recovery continues). When the person cannot ambulate, preventive measures may include compression stockings and anticoagulant medications.

See also COAGULATION; MYOCARDIAL INFARCTION; PLATELET AGGREGATION; POSTOPERATIVE CARE; STROKE; SURGERY BENEFIT AND RISK ASSESSMENT; WEIGHT LOSS AND WEIGHT MANAGEMENT.

pulmonary fibrosis A condition in which SCAR tissue replaces normal tissue in the alveoli, reducing the ability of the LUNGS to oxygenate the BLOOD. Many conditions of the lungs result in fibrosis, notably CYSTIC FIBROSIS and occupational PNEUMOCONIOSIS. Pulmonary fibrosis may also be idiopathic—that is, develop without an identifiable cause. Once the process of fibrosis begins in the lungs, it tends to be progressive. In many people the progression takes place over decades, resulting in slow decline of pulmonary function. Clubbing of the fingers is a characteristic indication of chronic HYPOXIA (insufficient oxygen reaching the tissues) such as results from pulmonary fibrosis.

Symptoms of pulmonary fibrosis include

- persistent dry COUGH
- DYSPNEA (shortness of breath) that worsens with exertion
- diminishing capacity for physical activity
- fatigue
- chest tightness, discomfort, or PAIN

The diagnostic path includes chest X-RAY, pulmonary function tests, and arterial blood gases. The pulmonologist may conduct additional imaging procedures, such as COMPUTED TOMOGRAPHY (CT) SCAN, to further assess structural changes in the lungs. BRONCHOSCOPY and lung biopsy may be necessary to rule out CANCER or to identify pathologic changes that characterize specific diseases.

Treatment depends on the underlying cause, if the diagnostic path can identify one. Generalized treatment may include CORTICOSTEROID MEDICATIONS to reduce INFLAMMATION, bronchodilator medications to relax and open the airways, and cough suppressants to relieve nonproductive coughing. These methods control symptoms and improve BREATHING in many people who have pulmonary fibrosis, especially in the early and middle stages of the condition. However, progressive pulmonary fibrosis typically results in RESPIRATORY FAILURE for which LUNG TRANSPLANTATION may be the only viable treatment option.

See also BRONCHIECTASIS; CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD); CYSTIC FIBROSIS AND THE LUNGS; INTERSTITIAL LUNG DISORDERS; NAILS.

R

rales See BREATH SOUNDS.

respiration rate The number of respiratory cycles a person completes in one minute. A typical healthy adult has a respiration rate of 15 to 20 per minute, measured by counting each inhalation or each exhalation (a respiratory cycle is one of each). Respiration rate normally is lower at rest and during sleep, and accelerates as well as intensifies with physical activity and exercise. Children have higher respiration rates than adults. The respiration rate typically increases with health circumstances such as INFECTION, FEVER, trauma, PAIN, and strong emotions such as fear. The brainstem regulates the respiration rate, in intimate coordination with other vital functions such as HEART RATE and BLOOD PRESSURE. The respiration rate remains at roughly a ratio of 1 to 4 with the heart rate (one breath for every four contractions of the HEART).

See also BREATHING; CARDIAC CYCLE.

respiratory cycle One repetition of the pattern of inhalation (BREATHING air into the LUNGS), OXYGEN–CARBON DIOXIDE EXCHANGE, and exhalation (breathing air out of the lungs). In health a typical adult completes 15 to 20 respiratory cycles a minute, called the RESPIRATION RATE. The brainstem regulates the respiratory cycle in response to feedback mechanisms from other body systems that indicate oxygen needs and consumption.

See also AEROBIC FITNESS; BREATHING EXERCISES; DYSPNEA; HYPERVENTILATION; TACHYPNEA.

respiratory failure The inability of the LUNGS to diffuse enough oxygen into the bloodstream to meet the body's needs. Respiratory failure may arise from end-stage pulmonary disease, extensive trauma, severe CARDIOVASCULAR DISEASE (CVD) or crisis (such as HEART ATTACK), neurologic damage or injury (such as SPINAL CORD INJURY, TRAUMATIC BRAIN INJURY [TBI], STROKE, or neurodegenerative disorder), or severe INFECTION (sepsis). Respiratory failure may be acute or chronic.

Acute respiratory failure is a life-threatening condition that results from the inability to breathe enough or the inability of the lungs to diffuse adequate amounts of oxygen into the blood, or a combination of both. Symptoms of acute respiratory failure typically are pronounced and include

- extreme DYSPNEA (shortness of breath or difficult BREATHING)
- CYANOSIS (bluish hue to the lips and SKIN)
- HYPOTENSION (low BLOOD PRESSURE)
- cardiovascular SHOCK

Treatment of acute respiratory failure requires oxygen administration and immediate resuscitative breathing or MECHANICAL VENTILATION; without prompt restoration of oxygenation, death is inevitable.

Chronic respiratory failure may also be life-threatening, though commonly the person accommodates the inadequate oxygenation through restricted physical activity and treatments such as OXYGEN THERAPY. Chronic respiratory failure is a consequence of progressive pulmonary disorders such as CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD). Symptoms of chronic respiratory failure may be activity related and often include

- persistent COUGH
- dyspnea, especially with exertion
- diminished cognitive ability or confusion

- cyanosis
- fatigue
- edema (swelling, typically in the hands and feet)

Doctors measure and assess chronic respiratory failure through blood levels of oxygen (which are low) and carbon dioxide (which are high). People who have chronic respiratory failure also commonly have PULMONARY HYPERTENSION. Treatment for chronic respiratory failure attempts to improve oxygenation through OXYGEN THERAPY and medications such as bronchodilators and some situations corticosteroids. The underlying disease and the person's response to therapy are key factors in determining the overall treatment approach. When chronic respiratory failure results from end-stage pulmonary disease, treatment options are limited. Some people are candidates for LUNG TRANSPLANTATION.

See also APNEA; ATELECTASIS; BREATH SOUNDS; BRONCHIECTASIS; OXYGEN–CARBON DIOXIDE EXCHANGE; SUDDEN CARDIAC DEATH.

S

silicosis An obstructive condition of the LUNGS that develops with repeated and usually long-term exposure to crystalline silica (silica dust). Silicosis is a disease of occupational exposure. The silica dust causes irritation and INFLAMMATION of the airways and lung tissue. SCAR tissue forms when the inflammation heals, resulting in fibrosis that gradually overtakes healthy lung tissue. The fibrosis continues extending through the lungs even after exposure ends.

Health experts identify three forms of silicosis:

- chronic silicosis, the most common form, results from long-term exposure (10 to 20 years or longer) and generally is present as a disease entity in the lungs for 5 to 10 years before symptoms lead to its diagnosis
- accelerated silicosis, which shows rapidly progressive symptoms after 5 to 10 years of exposure
- acute silicosis, which occurs with exposure to high concentrations of silica dust and shows symptoms within weeks to months of exposure

A secondary complication, progressive massive fibrosis, may occur with accelerated or chronic silicosis. In progressive massive fibrosis the scarring is severe and results in extensive destruction of lung tissue and loss of lung function.

The US Occupational Safety and Health Administration (OSHA) began regulating silica exposure in the 1990s and currently monitors silica levels as well as cases of silicosis. Employees who work in occupations with silica exposure should wear appropriate protective equipment including filtered respirators to limit as much as possible the amount of silica dust they breathe. About 200 people die each year in the United States as a consequence of silicosis.

Symptoms and Diagnostic Path

The primary symptoms of silicosis are chronic COUGH and DYSPNEA (shortness of breath) that worsens with exertion. People who have acute silicosis may also have FEVER and experience rapid, unintended weight loss. The diagnostic path includes chest X-RAY, imaging procedures such as COMPUTED TOMOGRAPHY (CT) SCAN, and pulmonary function tests. Characteristic findings with these diagnostic procedures in combination with a history of silica exposure allow the doctor to make a conclusive diagnosis.

People who have silicosis have high risk for developing TUBERCULOSIS, and many have latent (asymptomatic) tuberculosis when tested at the time of the silicosis diagnosis. Health experts recommend routine testing for tuberculosis as part of the diagnostic process for silicosis.

Treatment Options and Outlook

Treatment can only help manage symptoms such as cough. There are no specific treatments for the silicosis, and there is no known method of intervention to prevent the condition's progression. It is crucial to end the silica exposure to end further damage to the lungs, and for those who smoke cigarettes to stop. Treatment may also be necessary for tuberculosis in people who test positive, even if there are no symptoms of the INFECTION. The course of progression often extends over decades, though does result in persistent decline of pulmonary function. Prevention remains the most effective therapeutic approach.

Risk Factors and Preventive Measures

Occupational exposure is the risk factor for silicosis. Appropriate personal protective equipment in combination with work-site dust management methods has the potential to prevent nearly all cases of silicosis. New cases of silicosis have steadily declined in the United States since the implementation of OSHA regulations limiting exposure, a trend health experts expect to continue. Researchers believe the silica dust interferes with the IMMUNE SYSTEM's ability to protect against certain kinds of infection, notably tuberculosis. Health experts recommend annual tuberculosis testing for everyone diagnosed with silicosis.

OCCUPATIONS AT RISK FOR SILICOSIS

abrasive blasting	agricultural plowing
ceramics	foundry core room
foundry shakeout	glass etching
glass manufacturing	jack hammering
masonry work	mineral mining
pottery	quarry work
road construction	rock blasting
rock drilling	rock tunneling
sandblasting	soap and detergent manufacturing
stone chipping and crushing	stone grinding
stone cutting	

See also ANTHRACOSIS; ASBESTOSIS; BERYLLIOSIS; BYSSINOSIS; PNEUMOCONIOSIS.

smoking and pulmonary disease Cigarette smoking is the leading cause of health conditions affecting the LUNGS and accounts for 90 percent of LUNG CANCER in the United States. Cigarette smoking is also the leading cause of many forms of CARDIOVASCULAR DISEASE (CVD), including HYPERTENSION, ATHEROSCLEROSIS, ISCHEMIC HEART DISEASE (IHD), CORONARY ARTERY DISEASE (CAD), and PERIPHERAL VASCULAR DISEASE (PVD). Though the correlation between cigarette smoking and lung cancer has been known since the 1940s and widely publicized since the 1964 landmark report *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service*, nearly 49 million Americans currently smoke. About one in six has at least one significant health condition that is a direct consequence of smoking. The longer a person smokes, the higher the risk for developing a smoking-related health condition.

Smoking and Pulmonary Function

The first few puffs of every cigarette paralyze the cilia, the hairlike structures that line the airways and sweep mucus from the lungs. NICOTINE from the smoke immediately passes across the alveolar membrane into the BLOOD, entering the circulation within seconds. A potent central NERVOUS SYSTEM STIMULANT and vasoconstrictor, nicotine causes smooth MUSCLE fibers to contract, contributing to cerebrovascular and cardiovascular disease such as STROKE and HEART ATTACK. Nicotine remains active in the circulation for about 20 minutes after the last puff from the cigarette, keeping the airways constricted.

One of the most hazardous chemicals in cigarette smoke is carbon monoxide, which binds more strongly with HEMOGLOBIN than oxygen. Hemoglobin molecules will not release carbon monoxide to bind with oxygen, thus carbon monoxide blocks oxygen diffusion into the blood. Carbon monoxide levels in the blood can reach 5 to 7 percent with smoking a single cigarette, dropping OXYGEN SATURATION to near 90 percent. The other byproducts of combustion from cigarette smoke can result in direct toxicity to the lungs.

Smoking and Obstructive Lung Diseases

Tar and smoke particulates that enter the airways and lungs with each cigarette cause irritation and INFLAMMATION. Over time SCAR tissue replaces lung tissue as the body attempts to repair itself from repeated damage and protect itself from further damage. This scar tissue gradually destroys the alveoli and bronchioles, the lung's smallest structures, and eventually becomes pervasive within the lungs. The consequence is CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD), which accounts for more than 70 percent of pulmonary disease related to smoking. COPD is the leading reason for LUNG TRANSPLANTATION in the United States and is also the leading form of noncancer lung disease. Once the damage of COPD occurs, it is permanent.

Lung Cancer

Cigarette smoke contains about 4,000 identifiable chemicals, more than 60 of which are identified carcinogens (cancer-causing substances). Among them are tar, arsenic, polycyclic aromatic hydrocarbon (PAH) compounds, formaldehyde, and nitrosamines. Smoking accounts for more than 90 percent of LUNG CANCER in the United States. Among cancers, lung cancer is the leading killer of both men and women. Part of the reason the outlook is so poor for lung cancer is that by the time it shows symptoms it is fairly advanced and often has spread to other organs throughout the body.

Pulmonary Benefits of Smoking Cessation

Much, though not all, of the damage cigarette smoking does will gradually repair itself when the person no longer smokes. The rate of decline of lung function will slow, and chronic cough and sputum production often improve. Cardiovascular risk also drops significantly after smoking cessation. Risk for head and neck and lung cancers also decreases.

See also ANTISMOKING EFFORTS; ASBESTOSIS; ASTHMA; ENVIRONMENTAL CIGARETTE SMOKE; SMOKING AND HEALTH.

sputum The mucus and secretions the pulmonary tract produces, mixed with debris and foreign matter that enter the airways. Sputum is a normal body fluid, though excessive amounts of sputum often signal pulmonary disease. The color and consistency of sputum provide clues about the health of the LUNGS and airways, though are not reliable diagnostic characteristics by themselves. Sputum culture is the only way to know whether an INFECTION is bacterial. A reliable sputum culture requires deep coughing to bring sputum from within the lungs.

See also HEMOPTYSIS.

stridor See BREATH SOUNDS.

suffocation See ASPHYXIATION.

T–W

tachypnea An abnormally rapid RESPIRATION RATE. BREATHING is also usually shallow. The normal respiration rate for healthy adults is 15 to 20 respiratory cycles per minute. In tachypnea the respiration rate can be two to four times normal. Breathing may appear labored, and when the body is not able to meet its needs the person may look cyanotic (pale or bluish) if the tissues are receiving inadequate oxygen. Tachypnea is a symptom of numerous health conditions ranging from FEVER to serious INFECTION such as PNEUMONIA. In transient tachypnea of the newborn, an infant develops a pattern of tachypneic breathing that lasts 24 to 72 hours after birth. Doctors believe this form of tachypnea, which resolves without treatment or complications, occurs as a mechanism for the infant to clear residual AMNIOTIC FLUID from the LUNGS.

See also CYANOSIS; DYSPNEA; HYPERVENTILATION.

thoracentesis The removal of fluid from the pleural cavity (the space between the pleural surfaces of the lung and thoracic cavity). The doctor typically uses chest X-RAY, ULTRASOUND, or COMPUTED TOMOGRAPHY (CT) SCAN to assess the appropriate site for the thoracentesis and may use any of these imaging procedures to guide the process of the thoracentesis. After anesthetizing (numbing) the SKIN and tissues at the site, the doctor inserts a large-gauge needle between the ribs and into the pleural cavity to withdraw pleural fluid.

Thoracentesis may be diagnostic, in which case the doctor withdraws a small amount of fluid for laboratory examination of the cells and any pathogens it contains. The doctor may conduct diagnostic thoracentesis to evaluate circumstances such as

- CHEST PAIN and other symptoms that suggest PLEURISY or PLEURAL EFFUSION
- mesothelioma, a CANCER related to ASBESTOSIS or asbestos exposure
- identification of infection (bacterial or tuberculosis)
- staging of LUNG CANCER

Thoracentesis may also be therapeutic, such as to drain a major pleural effusion. Potential complications of thoracentesis include vasovagal NERVE stimulation that causes SYNCOPE (fainting) bleeding, INFECTION, bleeding, and PNEUMOTHORAX. Most procedures are uncomplicated and discomfort is usually mild and temporary.

See also ATELECTASIS; STAGING AND GRADING OF CANCER; THORACOTOMY.

thoracotomy A major OPERATION in which the surgeon opens the chest cavity to remove part or all of a lung. Surgeons most commonly perform thoracotomy to treat LUNG CANCER or severe trauma to the lungs. Other reasons for thoracotomy include LUNG ABSCESS that does not respond to antibiotic therapy, CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) in which there is significant alveolar destruction and lung volume resection may be of benefit, severe BRONCHIECTASIS with bleeding requiring resection of part of the lung, biopsy of lung tissue or suspected tumor, and LUNG TRANSPLANTATION. There are three kinds of thoracotomy:

- wedge resection removes a small segment of lung tissue
- lobectomy removes an entire lobe of the lung
- pneumonectomy removes a whole lung

In lung transplantation, the surgeon first performs pneumonectomy and then transplants the donor replacement lung. Thoracotomy entails a hospital stay of up to 10 days, depending on the kind of surgery, and a recuperation period of two to four months though some people can return to most of their normal activities within six to eight weeks. Additional treatment, such as RADIATION THERAPY or CHEMOTHERAPY for lung cancer, may extend the recuperation period.

Surgical Procedure

The doctor performs thoracotomy with the person under general ANESTHESIA. The placement and length of the incision depends on the kind of thoracotomy and the reason for performing it. The incision must be between the ribs, and the surgeon must either spread the ribs (using an instrument called a rib spreader) or remove a portion of rib to gain access to the thoracic cavity. The surgeon removes the intended segment, lobe, or entire lung, and places tubes that will drain air, BLOOD, and other fluids during HEALING. The operation may take two to six hours, longer for lung transplantation. The person then remains in the recovery room until the anesthesia wears off, with intensive nursing care to maintain BREATHING and other vital functions. Less invasive approaches that use fiberoptic scopes and a smaller incision are now an option, particularly for biopsies. Such MINIMALLY INVASIVE PROCEDURES allow quicker operative times and recuperation.

Risks and Complications

Because thoracotomy breaches the thoracic cavity, there are significant risks involved with this operation. The most common are bleeding, infection, and PNEUMOTHORAX. These risks are potentially life-threatening though are usually readily treatable and survivable. Complications include RESPIRATORY FAILURE and RECURRENCE of the circumstance that made the operation necessary. Removal of a complete lung results in the remaining structures of the thoracic cavity shifting position, which can alter HEART function, gastric (STOMACH) function, and breathing.

Outlook and Lifestyle Modifications

Many people spend the first 48 to 72 hours following surgery in the intensive care unit (ICU). MECHANICAL VENTILATION ensures that the remaining lung structure inflates fully to provide adequate oxygenation. As the healing process progresses the affected lung (after lobar resection), or remaining lung when the operation is pneumonectomy, expands to fill the thoracic cavity and pulmonary function improves. Most people can sustain strong pulmonary function with only one lung when the remaining lung is healthy and overall health is good. Lifestyle modifications and prognosis (outlook) vary with the underlying health condition.

See also SMOKING CESSATION; SURGERY BENEFIT AND RISK ASSESSMENT.

trachea The major airway leading from the THROAT to the LUNGS. The trachea extends about four and a half inches from the top of the throat to the center of the chest. The sternum (breastbone) in the front and the spine in the back protect the trachea for much of its length. The front of the trachea arches more than the back of the trachea, producing an oval rather than round tubular structure with a diameter (from side to side) of about an inch. The trachea terminates in two branches, the right main BRONCHUS that goes to the right lung and the left main bronchus that goes to the left lung.

The trachea is made of smooth MUSCLE tissue along the back wall with 16 to 20 C-shaped bands of CARTILAGE running along its length. The cartilage rings give the trachea stability and resistance against the pressure of air flow into and out of the lungs. Thousands of hairlike structures called cilia line the inner layer of the trachea, the tracheal epithelium. The cilia move in wavelike patterns to push secretions and foreign matter, such as dust and particles, out of the airways. The epithelial cells secrete mucus, which keeps the inner trachea moist. The mucus helps humidify the air as it flows into the lungs, and lubricates the air's passage. The mucus also traps foreign material so the cilia can sweep it from the airways. Coughing expels air rapidly and forcefully from the lungs, pushing SPUTUM (pulmonary mucus and the debris it contains) into the throat for removal from the body.

For further discussion of the trachea within the context of pulmonary structure and function

please see the overview section "The Pulmonary System."

See also ALVEOLUS; EPIGLOTTIS; TRACHEOSTOMY.

tracheostomy A surgical opening created in the TRACHEA to allow air to enter the LUNGS, bypassing the upper THROAT and MOUTH. A tracheostomy may be temporary or permanent. The doctor may perform a tracheostomy when extensive surgery such as to treat laryngeal CANCER results in removing the shared structures of the throat that allow air to flow into the trachea, or when neurologic damage necessitates long-term MECHANICAL VENTILATION. SWALLOWING DISORDERS that impede normal epiglottal function (which keeps food and water from entering the trachea) and SLEEP APNEA that fails to respond to other treatments may also make tracheostomy necessary.

In most cases the doctor performs tracheostomy with the person under general ANESTHESIA. The incision is typically between the second and third or third and fourth tracheal cartilages in the front of the neck, to make an opening about an inch to an inch and a quarter (2 to 3 centimeters) in length. The doctor then inserts a tube into the opening to maintain a passageway into the trachea. The kind of tube and finishing process for the incision depends on whether the doctor intends the tracheostomy to be temporary or permanent. An inflatable cuff may hold the tracheostomy tube in place, though some designs are cuffless. Most tracheostomies use an inner and outer cannula (tube), allowing removal of the inner cannula for cleaning. A device called an obturator allows changing of the entire tracheostomy tube and guides reinsertion of the new tube.

Most people who are conscious are able to resume regular eating and speaking. Speech requires closing off the tracheostomy tube to bring air through the throat and past the VOCAL CORDS. Potential complications of tracheostomy include bleeding after the OPERATION, INFECTION, and blockage of the tube with mucus or foreign material that enters the tube from the outside. Conscientious hygiene, including daily cleansing of the tracheostomy site and tube, is essential. It is important to humidify the air breathed into the tracheostomy, such as with a room humidifier or moist gauze (rewetted as needed) placed over the tube opening. Home health nursing agencies provide education and training in how to care for a tracheostomy for people who have tracheostomies and their family members or caregivers. Even a long-term stoma will heal closed should the person's condition improve such that normal BREATHING ability returns and the doctor can remove the tube.

See also EPIGLOTTIS; OXYGEN THERAPY; SPINAL CORD INJURY; TRAUMATIC BRAIN INJURY (TBI).

wheeze See BREATH SOUNDS.

THE IMMUNE SYSTEM AND ALLERGIES

The IMMUNE SYSTEM protects the body from INFECTION. Allergies represent an inappropriate response from the immune system toward harmless substances. Doctors (MDs and DOs) who treat conditions of the immune system may be internists or immunologists. Doctors who specialize in treating allergies are allergists, and those who specialize in treating RHEUMATOID ARTHRITIS and related AUTOIMMUNE DISORDERS are rheumatologists.

Structures of the Immune System

LYMPH
lymph nodes
B-CELL LYMPHOCYTE
  plasma cell
  memory B-cell
T-CELL LYMPHOCYTE
  cytotoxic (killer) T-cell
  memory T-cell
  helper T-cell
  suppressor t-cell
NATURAL KILLER (NK) CELL
complement factors
MONOCYTE
MACROPHAGE
GRANULOCYTE
  basophil
  eosinophil
  neutrophil
MAST CELL
M cell
adenoids
tonsils
THYMUS
PEYER'S PATCHES
APPENDIX
MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT)
SKIN-ASSOCIATED LYMPHOID TISSUE (SALT)
NOSE-ASSOCIATED LYMPHOID TISSUE (NALT)
BRONCHIAL-ASSOCIATED LYMPHOID TISSUE (BALT)
GUT-ASSOCIATED LYMPHOID TISSUE (GALT)
VASCULAR-ASSOCIATED LYMPHOID TISSUE (VALT)

Functions of the Immune System

The immune system's role is to protect the body from infection. Infection, from the immune system's perspective, is any activity from foreign entities that causes damage to cells. It does so through a complex and intricate integration of organs, tissues, cells, and molecules.

Each day the BONE MARROW releases billions of monocytes and granulocytes, also called polymorphonuclear cells (PMNs), into the BLOOD circulation. Monocytes circulate in the blood for about 24 hours and then migrate into the LYMPH tissues, LIVER, and the various MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT) structures throughout the body. Known as macrophages after their migration, these cells participate in ANTIGEN processing as well as continued PHAGOCYTOSIS (consumption of cellular debris). Granulocytes (neutrophils, basophils, and eosinophils) are instrumental in the body's inflammatory response, which is integral to HEALING in normal immune function as well as responsible for much of the distress of a HYPERSENSITIVITY REACTION—ALLERGY—when the immune system malfunctions.

The workhorse cells of the immune system are the lymphocytes, which from birth divide into two camps: B-cell lymphocytes, which patrol the blood and lymph on the alert for invaders, and T-cell lymphocytes, which respond to the call of B-cell lymphocytes when invaders penetrate the body's barriers. B-cell lymphocytes come to maturity in the bone marrow and regulate ANTIBODY-MEDIATED IMMUNITY. T-cell lymphocytes come to maturity in the THYMUS and regulate CELL-MEDIATED IMMUNITY. Lymphocytes circulate in the blood and the lymph, and also reside in lymph organs and tissues throughout the body. The SPLEEN contains about half the body's supply of lymphocytes.

Perhaps more than any other system of the body the immune system is one of molecular function. The entire function of the immune system centers on the ability of immune cells to distinguish cells that belong to the body—self cells—from cells that do not belong to the body—nonself cells. It does so through molecular mark-

ers called antigens. Lymphocytes, natural killer (NK) cells, macrophages, and the complement factors—a collection of substances that, when activated (the COMPLEMENT CASCADE), form potent chemical structures—key onto these antigens like lasers onto targets. Cells bearing self antigens continue unimpeded about their business in the body. Those bearing nonself antigens are tagged for destruction by another set of molecular markers, antibodies, that specialized B-cell lymphocytes called PLASMA cells produce. Each individual antigen generates a different ANTIBODY; millions of antibodies circulate in the blood and lymph.

Filling out the immune system's defense are specialized clusters of lymphoid tissue that line each point of access into the inner body: SKIN, NOSE, airways, gastrointestinal system, and even the blood vessels. These clusters—known collectively as the mucosa-associated lymphoid system—are like guard posts protecting the body's vulnerabilities. MALT contains abundant populations of lymphocytes, mast cells, and macrophages that detect and intercept millions of microbes, viruses, toxins, and irritants before they can breach the inner body.

Health and Disorders of the Immune System

In health the immune system is an amazing network of cells and molecules that patrol every pathway of the body. Most of the time, the immune system goes about protecting and ridding the body from invading pathogens without drawing any notice to its activities. Only when the immune system is too efficient—causing hypersensitivity reactions or autoimmune disorders—or ineffective—allowing infection or cancer—does its existence become unpleasantly apparent.

Inflammation: the front line The immune system's first response primary weapon is INFLAMMATION. Inflammation floods the affected tissues with infection-fighting molecules. Plasma, the liquid component of blood, carries these molecules and delivers them to the site of the infection. The familiar swelling of inflammation is the body's "caution: IMMUNE RESPONSE at work" sign. Inflammation causes PAIN, which encourages if not forces limited activity of the affected area. This allows plasma to thoroughly saturate the area, speeding healing and recovery. Inflammation may also cause FEVER, yet another inducement to take it easy. As unpleasant as these symptoms are, they serve notice that the immune system is on task.

Autoimmune disorders: attacking self cells Inflammation sometimes gets out of hand. The immune response may not recognize that its task is over. Inflammation may become so severe that it impedes the flow of blood, threatening the well-being of the body in other ways. ANTIBIOTIC MEDICATIONS may be necessary to bring in another flank of attack against the PATHOGEN. Or a malfunction of the immune system may erroneously mark self cells as invaders, directing the immune response to attack structures of the body that contain the cells. These are autoimmune disorders—such as RHEUMATOID ARTHRITIS, SYSTEMIC LUPUS ERYTHEMATOSUS (SLE), and type 1 DIABETES.

Allergies: mistaken identity About 50 million Americans have allergies, mostly to pollens, molds, foods, animal dander, and medications. More than 18 million adults and 7 million children in the United States have seasonal allergies that cause ALLERGIC RHINITIS, ALLERGIC ASTHMA, and ALLERGIC CONJUNCTIVITIS—a triad of hypersensitivity reactions known collectively as hay fever. Another 9 million Americans, two thirds of them children, have FOOD ALLERGIES.

With allergies, the immune system turns not against the body itself but against harmless substances the body encounters, misidentifying them as dangerous intruders. Plasma cells then generate antibodies that perceive the molecular markers of these substances—allergens—as harmful and launch an immune response upon detecting their presence. Hypersensitivity reactions cause symptoms that range from annoying to life-threatening. It often is not possible to escape the reach of an ALLERGEN; treatment becomes the only recourse for relieving symptoms.

Immunodeficiency: AWOL Sometimes the immune system fails to function properly because key components are deficient or missing. Genetic errors may result in an absence of T-cell lymphocytes, B-cell lymphocytes, complement factors, immunoglobulins, or other substances necessary to integrate the immune response. Such deficits increase vulnerability to infection and, when severe, threaten life. The most significant acquired immunodeficiency is HIV/AIDS, which results from

infection with a VIRUS that hijacks and then destroys certain T-cell lymphocytes. There are treatments but as yet no cures for most immunodeficiencies, including HIV/AIDS.

Cancer: treacherous betrayal One of the greatest mysteries about immune function is cancer, the unregulated growth of cells. Ordinarily the immune response detects and destroys abnormal cells in the body, even when they are self cells. Cancer represents the ultimate betrayal of the immune system by self cells that dangerously mutate yet maintain enough self-antigens to escape detection. There comes a point in a cancer's development when tumor necrosis factors (TNFs), potent antitumor substances, are no longer able to squelch the errant growth. Some tumors seem able to avoid activating TNFs at all.

DISORDERS OF IMMUNE FUNCTION

ALLERGIC ASTHMA	ALLERGIC CONJUNCTIVITIS
ALLERGIC DERMATITIS	ALLERGIC RHINITIS
ANAPHYLAXIS	ANGIOEDEMA
ANKYLOSING SPONDYLITIS	ATOPY
autoimmune ADDISON'S DISEASE	autoimmune HEPATITIS
BULLOUS PEMPHIGOID	COMMON VARIABLE IMMUNODEFICIENCY (CVID)
dermatomyositis	DISCOID LUPUS ERYTHEMATOSUS (DLE)
DIABETES type 1	GRAFT VS. HOST DISEASE
FOOD ALLERGIES	Hashimoto's THYROIDITIS
GOODPASTURE'S SYNDROME	HYPERSENSITIVITY REACTION
GRAVES'S DISEASE	INFLAMMATORY BOWEL DISEASE (IBD)
HIV/AIDS	MULTIPLE MYELOMA
IgA NEPHROPATHY	MYASTHENIA GRAVIS
LEUKEMIA	PARTIAL COMBINED IMMUNODEFICIENCY (PCID)
lymphoma	POLYMYOSITIS
MULTIPLE SCLEROSIS	RHEUMATOID ARTHRITIS
organ transplant rejection	SCLERODERMA
PEMPHIGUS	SJÖGREN'S SYNDROME
pernicious ANEMIA	SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)
REITER'S SYNDROME	
SARCOIDOSIS	
SEVERE COMBINED IMMUNODEFICIENCY (SCID)	
VASCULITIS	

Traditions in Medical History

Until the discovery of BACTERIA and viruses in the 19th century, doctors had little understanding for how the body contained and fought infection. Recognizing fever as a sign of healing led to efforts to "sweat out" the infection. Bloodletting was long a tradition for treating all kinds of ailments. The body's natural ability and tendency to overcome most infections gave credence to these and other methods. With the recognition of microbes and their role in pathogenesis (process of infection), research leapfrogged to greatly expanded understanding of immune system components and their functions.

Contemporary research has shown that some pre–MICROBE era therapeutic efforts have merit for bolstering immune function. Herbs such as ECHINACEA, GOLDENSEAL, and FEVERFEW boost immune response. Licorice root, turmeric, ginger, white willow (the forerunner of aspirin), witch hazel, and GREEN TEA are effective anti-inflammatory agents. Vitamins and minerals aid the intricate biochemical conversions essential for immune function. Antioxidants clear away molecular debris. Nature, as it turns out, staunchly supports the immune system.

Breakthrough Research and Treatment Advances

One of the most significant breakthroughs in disease management came with the introduction of vaccines in the mid-20th century. Before 1950, infection was the leading cause of death among Americans. The debut of antibiotic medications at the end of World War II was a tremendous stride in the ability to fight bacterial infections. But antibiotics are ineffective against viruses. In 1950 the viral infection POLIOMYELITIS was the leading cause of PARALYSIS among Americans; a decade later vaccination had made polio a rare condition. The World Health Organization (WHO) declared SMALLPOX, the first infection for which there was a successful VACCINE, eradicated in nearly all parts of the world in 1970—another landmark triumph in manipulation of the immune system to protect the body against infection without actually acquiring the infection. Today vaccines have made rare many diseases that were once common killers.

As researchers learn more about immune function and disease processes, the emphasis is shifting from treating the disease to preventing its development. Most CARDIOVASCULAR DISEASE (CVD), the leading cause of death among Americans, stems from a combination of lifestyle factors and inflammatory response. Though doctors have long

believed ATHEROSCLEROSIS (deposits of atherosclerotic plaque within the walls of the arteries) caused inflammation, recent research indicates the reverse is the case: inflammation attracts atherosclerotic deposits. Though further research is necessary to substantiate these findings, the result could be an entirely new perspective and approach for preventing cardiovascular disease.

Other research focuses on manipulating the immune system to "turn off" autoimmune disorders such as type 1 diabetes and rheumatoid arthritis, conditions that contribute to significant disability. Cancer research also is looking to the immune system to treat, cure, and prevent cancer. MONOCLONAL ANTIBODIES (MABS), genetically engineered molecules, can be laced with radioactive isotopes and targeted to the antigens on the cell surfaces of cancer cells, selectively killing them without damaging healthy cells. Researchers also believe it is possible to "teach" the immune system to recognize cancer cells and use its own resources to destroy them. Cancer vaccines are one direction of such research; molecular manipulation is another.

A

active immunity Long-term, acquired immune protection. Active immunity, also called acquired immunity, results from fighting an INFECTION or receiving a VACCINE that stimulates ANTIBODY response. In many circumstances active immunity is lifelong.

See also ANTIBODY-MEDIATED IMMUNITY; CELL-MEDIATED IMMUNITY; PASSIVE IMMUNITY.

aging, effects on immune response At birth the IMMUNE SYSTEM is fairly undeveloped. The infant relies largely on the carryover of maternal immune components for about the first six weeks of its life, while the infant's body builds its own immune system. By age four months, maternal IMMUNITY wears off and the infant's immune system is on its own (though an infant who is BREASTFEEDING continues to receive antibodies and limited immune support from his or her mother). Immunity reaches full STRENGTH in early childhood, a level at which it continues until about age 40.

After age 40, the effectiveness of the immune system begins to diminish. T-cell lymphocytes and macrophages respond more slowly. Levels of complement (protein factors essential for ANTIBODY–ANTIGEN binding) and of antibodies drop off. The immune system is slower to differentiate B-cell lymphocytes to antigen-producing PLASMA cells, and plasma cells produce lower quantities of antibodies. The immune response to disease as well as to vaccines becomes slower and less effective, increasing susceptibility to serious INFECTION (such as INFLUENZA and PNEUMONIA) from pathogens. The amounts and activity of MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT) decrease in areas such as the LUNGS, further reducing the body's ability to reject infection from invading pathogens. Decades of exposure to antigens mean more lymphocytes are sensitized for specific antigens, leaving fewer to become sensitized to new antigens. The IMMUNE RESPONSE summons T-cell lymphocytes less quickly to the scene of an infection.

Changes in antigens and antigen recognition also occur, resulting in a decreased ability of the immune system to distinguish between self and nonself antigens. Cells may acquire a mix of antigens that makes them appear foreign, initiating an inappropriate immune response (autoimmune disorder) that damages an organ or structure. Or the immune system may fail to detect the change in antigens on the surfaces of cell membranes of cells that become cancerous, allowing cancer tumors to develop. AUTOIMMUNE DISORDERS and cancer consequently become more common with advancing age.

Measures to prevent infection can help offset age-related immune changes to some degree. Diligent HAND WASHING and avoiding exposure to other people who have COLDS or influenza may prevent the spread of these infections. ECHINACEA and GOLDENSEAL are herbal remedies that can boost immune function after an exposure to common pathogens. GAMMAGLOBULIN may boost the immune response in circumstances such as exposure to HEPATITIS. Older people often benefit from more aggressive antibiotic therapy—ANTIBIOTIC MEDICATIONS administered early in the infection process—to help them fight infections they do develop.

See also ANTIBODY-MEDIATED IMMUNITY; CELL-MEDIATED IMMUNITY; COMPLEMENT CASCADE; HEALING; IMMUNOSENESCENCE; LYMPHOCYTE; MACROPHAGE; T-CELL LYMPHOCYTE.

allergen A harmless substance, also called a hapten, that causes an exaggerated response from the

IMMUNE SYSTEM called a HYPERSENSITIVITY REACTION. For reasons researchers do not fully understand, the immune system produces antibodies for the substance that result in the IMMUNE RESPONSE perceiving the substance as a foreign invader. When the allergen contacts or enters the body, the antibodies attack it. Nearly any substance can be an allergen. DESENSITIZATION is a treatment for allergies that exposes the person to progressive doses of the allergen to increase the body's tolerance for the presence of the allergen and diminish the hypersensitivity reaction.

COMMON ALLERGENS

almonds	animal dander	aspirin (salicylates)
bee stings	cashews	cockroaches
dust and dust mites	eggs	fish
fragrances and perfumes	fungi	grasses
lanolin	latex	milk
molds	nickel	peanuts
pecans	penicillin	pollens
shellfish	smoke	strawberries
SOY	sulfa	wheat

See also ALLERGY; ALLERGY TESTING; ANAPHYLAXIS; ANTIBODY; ANTIGEN; ASTHMA; LIVING WITH ALLERGIES; MULTIPLE CHEMICAL SENSITIVITY SYNDROME.

allergic asthma A HYPERSENSITIVITY REACTION (allergic reaction) that involves the airways (bronchi). allergic ASTHMA is a type I or IMMUNOGLOBULIN E (IgE) reaction. Mast cells in the bronchial membranes release HISTAMINE, PROSTAGLANDINS, and LEUKOTRIENES. These substances cause itching and swelling of the bronchial membranes, resulting in wheezing and the sensation of chest tightness.

Cockroach droppings are the most frequent cause of allergic asthma. Other common allergens for allergic asthma include pollens (trees, grasses, and weeds), dust and dust mites, cigarette smoke, molds, and pet dander (especially cat dander). About 70 percent of people who have allergic asthma also have ALLERGIC RHINITIS, also called seasonal allergies or hay FEVER.

The diagnostic path focuses on separating allergic from nonallergic asthma. Though the symptoms are the same, the mechanisms and treatment approaches are different. Symptoms of allergic asthma include wheezing, shortness of breath (DYSPNEA), sensation of being unable to get enough air, and coughing. A severe hypersensitivity reaction, ANAPHYLAXIS, may occur if the bronchi swell enough to prevent the flow of air into the LUNGS.

ANAPHYLAXIS is a potentially life-threatening condition that requires immediate care from a doctor or hospital emergency department.

Treatment for allergic asthma may include oral and inhaled ANTIHISTAMINE MEDICATIONS, corticosteroid medications, and leukotriene receptor antagonist medications. Omalizumab (Xolair), a monoclonal antibody administered via subcutaneous injection, dramatically drops IgE levels in the BLOOD circulation, effectively stopping the hypersensitivity reaction before it causes symptoms. The most effective treatment is avoiding known or suspected allergens, though this is not always possible. ALLERGY TESTING can determine the specific allergens responsible for symptoms. DESENSITIZATION, in which the allergist exposes the person to small but increasing doses of the allergen over time, can help reduce the immune response to the allergen.

See also ALLERGIC CONJUNCTIVITIS; ALLERGIC DERMATITIS; ALLERGY; ANTIGEN; ATOPY; BREATH SOUNDS; CYTOKINES; LIVING WITH ALLERGIES; MONOCLONAL ANTIBODIES (MABS).

allergic conjunctivitis A type I (IMMUNOGLOBULIN E [IgE]) HYPERSENSITIVITY REACTION, commonly called an allergic reaction, that affects the membranes that line the inner eyelids (conjunctiva). Sometimes the irritation also reddens the white part of the eye (sclera). Allergic CONJUNCTIVITIS features red and swollen conjunctiva with excessive tearing and itching of the eyes and sometimes a white discharge. PHOTOPHOBIA (heightened sensitivity to light) is common. Because these symptoms also suggest viral or bacterial conjunctivitis (pink eye), which are infections, particularly when the discharge is yellow or green, a doctor should examine the eyes and assess the symptoms to make the correct diagnosis. Treatment differs according to the cause.

EYE irritation that interferes with vision, causes PAIN, or follows injury to the eye requires a doctor's prompt evaluation.

The most common form of allergic conjunctivitis develops seasonally when airborne pollens are high. Some people develop allergic conjunctivitis with exposure to allergens such as dust and pet dander (especially cat dander) as part of a broader ALLERGY picture. People who have seasonal allergies (ALLERGIC RHINITIS), ALLERGIC ASTHMA, or other ATOPY conditions may have a GENETIC PREDISPOSITION for type I hypersensitivity reactions that puts them at higher risk for developing allergic conjunctivitis as well.

Treatment for allergic conjunctivitis combines avoiding the responsible ALLERGEN with EYE drops that contain an antihistamine or, for severe symptoms, a corticosteroid (anti-inflammatory medication that suppresses the IMMUNE RESPONSE). ANTIHISTAMINE MEDICATIONS neutralize the histamine responsible for the allergic response. Systemic antihistamine medications (allergy relief products) may also help, especially when there are accompanying allergy symptoms such as allergic rhinitis. Natural tears eye drops can restore moisture to eyes that are scratchy and dry. Allergic conjunctivitis generally resolves when exposure to the allergen ends, which may be the end of allergy season when seasonal allergies (hay fever) are responsible.

See also ALLERGIC DERMATITIS; DRY EYE SYNDROME; INFECTION; LIVING WITH ALLERGIES.

allergic dermatitis A HYPERSENSITIVITY REACTION (allergic reaction) that affects the SKIN, usually in response to contact with an ALLERGEN. As with all hypersensitivity reactions, the first exposure to the allergen produces no symptoms. In reaction to the exposure, however, the IMMUNE SYSTEM produces antibodies for the allergen. Subsequent exposures to the allergen then do produce symptoms. Abundant immune cells reside in the epidermis, the inner layer of skin that contains living cells, to react to the allergen.

Most allergic dermatitis is a type IV, or delayed, hypersensitivity reaction. Symptoms generally affect only the area of contact and begin to emerge 24 to 36 hours after the contact, though may start within hours to a week later. Sometimes there can be repeated exposure before the hypersensitivity reaction occurs, though most commonly the second exposure triggers the ALLERGY.

A less common but more severe form of reaction is atopic dermatitis, a chronic type I (IMMUNOGLOBULIN E [IgE]) hypersensitivity reaction. Atopic DERMATITIS, commonly called eczema, tends to occur in people who have other chronic hypersensitivity conditions such as ALLERGIC ASTHMA and ALLERGIC RHINITIS. GENETIC PREDISPOSITION is the most significant risk factor for atopic dermatitis. Often there is no apparent contact allergen that sets off an atopic dermatitis attack, and symptoms may continue for several weeks to months or appear to never quite go away.

POISON IVY, POISON OAK, AND POISON SUMAC

The blistering, itchy RASH that some people develop with exposure to poison ivy, poison oak, and poison sumac is an allergic reaction to the resins on the surface of these plants. Repeated contact creates as well as intensifies sensitivity. In a highly allergic person, a reaction may occur through contact with clothing that came into contact with the resins. Contrary to popular belief, the fluid in the rash's blisters does not spread the irritation. The rash appears to spread because the person's sensitivity to the resin increases even as the allergic reaction unfolds.

Symptoms and Diagnostic Path

Allergic dermatitis, sometimes called allergic contact dermatitis, results in URTICARIA (hives) or RASH, often along with itching. BLISTER formation is common. The diagnosis is fairly straightforward when the person knows he or she has had contact with a known allergen. It is sometimes difficult to distinguish allergic dermatitis from other forms of dermatitis. In such situations ALLERGY TESTING, in which the allergist places small amounts of suspect substances in patches on the skin, can often determine the responsible allergen. Many substances, such as detergents and cleaning chemicals, can cause contact dermatitis through direct damage to the cells of the skin. Though symptoms are similar to those of allergic dermatitis, the irritation occurs

as a direct action of the substance rather than as a hypersensitivity reaction.

Treatment Options and Outlook

Treatment may include calamine lotion and cool baths or compresses to relieve itching in combination with oral ANTIHISTAMINE MEDICATIONS or CORTICOSTEROID MEDICATIONS to interrupt the immune response. Cool baths or compresses with colloidal oatmeal can soothe irritated skin. Avoiding further exposure to the allergen prevents subsequent reactions and may, over time, allow the immune response to lessen in severity.

Risk Factors and Preventive Measures

Latex, nickel, chromates, and the dyes in permanent hair coloring solutions are the most common causes of allergic dermatitis. Numerous metal objects, including stainless steel and chrome plating, contain nickel. Spandex contains latex; spandex clothing such as undergarments and athletic wear may cause hypersensitivity reaction in people who are allergic to latex. Chromates, chemicals used in tanning leather, are common in leather shoes, belts, and clothing. The allergen in permanent hair dyes is a chemical called paraphenylenediamine (PPDA), which sometimes is also present in some dyed clothing though is not commonly used in fabric dyes in the United States. The risk for allergic dermatitis is particularly high among people who work in jobs with constant exposure to these common allergens.

See also ALLERGIC ASTHMA; ALLERGIC CONJUNCTIVITIS; ATOPY; LIVING WITH ALLERGIES; OCCUPATIONAL HEALTH AND SAFETY; SKIN-ASSOCIATED LYMPHOID TISSUE (SALT); WHEAL.

allergic rhinitis A HYPERSENSITIVITY REACTION to inhaled allergens. Allergic rhinitis, also called seasonal rhinitis or hay FEVER, affects the mucous membranes inside the NOSE (nasal mucosa). Allergic rhinitis affects about 40 million adults in the United States, making it one of the most common hypersensitivity reactions. The condition tends to develop in childhood and continue through adulthood, though some people who have allergic rhinitis as children seem to outgrow their sensitivities as they become adults.

MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT) infiltrates the nasal mucosa. Within the MALT are numerous mast cells, the surfaces of which harbor IMMUNOGLOBULIN E (IgE) antibodies. These antibodies react within hours to the presence of airborne allergens such as pollens. Allergic rhinitis is most common in the spring and the fall, though some people also experience symptoms in the summer, depending on what allergies they have. Allergic rhinitis is primarily a type I (IgE) hypersensitivity reaction, in which symptoms developing fairly immediately after contact with the ALLERGEN. The most common allergens associated with allergic rhinitis are tree pollens, grass pollens, and weed pollens. Other potential allergens include dust mites, pet dander, and other substances that are continuously present in the environment.

Symptoms and Diagnostic Path

The symptoms of rhinitis range from mild to debilitating. The classic symptoms occur in response to the presence of allergens and include

- nasal congestion
- itching
- sneezing
- RHINORRHEA (runny nose)

Some people also develop

- swollen, itchy, reddened eyes (ALLERGIC CONJUNCTIVITIS)
- dark circles under the eyes ("allergic shiners")
- OTITIS media (middle ear INFECTION)
- PHARYNGITIS (sore THROAT) from postnasal drip (mucus draining down the back of the throat)
- physical irritation of the nose due to frequent sneezing, blowing, and rubbing

The doctor makes the diagnosis based on the presentation of symptoms and the person's description of how the symptoms develop and how long they last.

Treatment Options and Outlook

Treatment combines avoiding the allergen when possible with medications to control symptoms.

Such medications typically include antihistamine nasal sprays, corticosteroid nasal sprays, oral ANTIHISTAMINE MEDICATIONS, and oral decongestant medications. Another classification of DRUG that is sometimes effective for allergic rhinitis is the leukotriene receptor antagonist, which blocks the action of LEUKOTRIENES (other chemicals that mediate the IMMUNE RESPONSE). The leukotriene receptor antagonist medication approved for use in the United States is montelukast (Singulair). Cromolyn sodium nasal spray targets mast cells, reducing their ability to release immune mediator chemicals such as histamine, PROSTAGLANDINS, and leukotrienes. DESENSITIZATION, commonly called allergy shots, is an option for some people. Desensitization works by exposing the IMMUNE SYSTEM to small amounts of the allergen over time to retrain the immune response to ignore the allergen.

Older antihistamine medications such as diphenhydramine (Benadryl) are very effective though cause drowsiness. Newer antihistamine medications such as loratadine (Claritin) are equally effective for most people and cause significantly less drowsiness. Antihistamines block the action of histamines, chemicals that mediate (initiate and facilitate) the processes of the immune response that result in the symptoms. Most antihistamines are available as OVER-THE-COUNTER (OTC) DRUGS that do not require a doctor's prescription. GINGER, available in various preparations, contains a mild antihistamine.

Oral decongestant medications available over the counter in the United States are pseudoephedrine and phenylephrine, though there are several OTC decongestant nasal sprays. Many OTC allergy products combine a decongestant with an antihistamine. Decongestants work by constricting the BLOOD vessels in the nasal mucosa, reducing the availability of fluid to the tissues. Chronic or long-term use of decongestants can result in rebound congestion, a condition in which the nasal membranes swell in the absence of the decongestant. Nose drops and nasal sprays containing saline (salt solution) are often as effective in relieving congestion. They work by soothing the nasal mucosa and flushing away topical irritants, including allergens.

Risk Factors and Preventive Measures

Allergic rhinitis is very common, affecting 20 percent of the American adult population. The most effective measure to reduce symptoms is to limit or eliminate exposure to the allergens that trigger the hypersensitivity response. Many people are able to mitigate symptoms by using allergy medications regularly for the duration of the allergy season.

There appears to be a GENETIC PREDISPOSITION for chronic allergic rhinitis, also called atopic rhinitis, which has more extensive symptoms that tend to be more perennial (ongoing) than seasonal. People who have atopic rhinitis have increased risk for other atopic conditions such as ALLERGIC ASTHMA (also called atopic asthma), atopic CONJUNCTIVITIS, and atopic DERMATITIS. A flare of symptoms in one atopic condition often brings on symptoms in another.

See also ALLERGIC DERMATITIS; ANTIBODY; CORTICOSTEROID MEDICATIONS; IMMUNOTHERAPY; LIVING WITH ALLERGIES; MAST CELL; SINUSITIS.

allergy An abnormal sensitivity to an ordinarily harmless substance, called an ALLERGEN, that produces a HYPERSENSITIVITY REACTION (allergic reaction) in response to the IMMUNE SYSTEM's detection of the substance's presence. A person can have an allergy to nearly any substance. Though researchers understand the mechanisms of hypersensitivity reaction, they do not know what causes the immune system to determine the substance is a potential invader. The first exposure to the substance activates an immune response that stimulates B-lymphocytes (specialized white BLOOD cells) to produce antibodies. Second and subsequent exposures engage the ANTIBODY response, in which the antibodies bind with molecules bearing the allergen to mark them for destruction.

Allergies are common. Symptoms vary according to the allergen. Some symptoms remain localized, affecting only a distinct part of the body (such as in ALLERGIC DERMATITIS or ALLERGIC RHINITIS). Others are systemic, affecting the body as a whole (such as hypersensitivity reaction to a drug or a food item). A severe hypersensitivity reaction can cause life-threatening swelling of the THROAT and airways (ANAPHYLAXIS).

See also ALLERGIC CONJUNCTIVITIS; ALLERGY TESTING; ANGIOEDEMA; ASTHMA; FOOD ALLERGIES; LIVING WITH ALLERGIES.

allergy testing Diagnostic procedures to determine the allergens responsible for HYPERSENSITIVITY REACTION. The most specific ALLERGY test is the allergy SKIN test, also called a scratch test or a patch test. For this test, the allergist uses the inside of the arm or a section of the back to expose the body to suspected allergens. The allergist places a small drop of a solution containing the ALLERGEN on a marked spot on the skin, then uses a sterile picklike instrument to scratch the surface of the skin. This exposes the IMMUNE SYSTEM to the suspected allergen. If a WHEAL (raised welt) forms on the site within 15 minutes, the test is positive for the allergen. For a typical allergy skin test, the allergist may test a number of substances at the same time, each on a different site on the skin. The allergy skin test tells the allergist the precise allergies an individual has. The allergy skin test helps the allergist strategize the most effective treatments and is necessary before DESENSITIZATION treatments.

Though it is rare, a person who has a strong allergy may have an intense reaction during an allergy SKIN test, including ANAPHYLAXIS, that requires urgent medical treatment.

A radioallergosorbent test (RAST) is a blood test that measures the amount of IMMUNOGLOBULIN E (IgE) in the BLOOD circulation when allergy symptoms are present. An amount higher than normal level of serum IgE indicates a hypersensitivity reaction. The RAST does not identify the specific allergen. There is no risk for the RAST to cause a hypersensitivity reaction because it does not expose the person to any allergens.

A food-elimination diet is the preferred allergy test to identify potential FOOD ALLERGIES. The person eliminates specific foods from his or her diet for several weeks, then reintroduces them one at a time and notes whether there are corresponding symptoms. An important part of a food-elimination diet is keeping an accurate food diary that records symptoms and other perceptions during the test. This allergy test is somewhat subjective, though often results in connecting specific foods with allergy symptoms. Another test for food allergies is the food challenge, which takes place in a hospital. The allergist gives the person certain foods, often mixed with other foods, without the person knowing, then observes and documents any symptoms that develop. There is a risk that the food challenge may cause a hypersensitivity reaction that would require immediate medical intervention; this is why the test takes place in a hospital or other emergency-ready facility.

See also ALLERGEN; ALLERGIC CONJUNCTIVITIS; ALLERGIC DERMATITIS; ALLERGIC RHINITIS; ANAPHYLAXIS.

anaphylaxis A severe HYPERSENSITIVITY REACTION (allergic reaction) in which the tissues of the throat swell, preventing air from getting to the LUNGS. Anaphylaxis, also called anaphylactic shock, is a type I hypersensitivity reaction that often develops rapidly, within minutes to an hour of exposure to the ALLERGEN. Hives, ANGIOEDEMA, and airway spasms are the most common symptoms. Some people also experience numbness or tingling of the lips and MOUTH. Though anaphylaxis can be life-threatening, with prompt and appropriate treatment it is seldom fatal.

The first line of treatment is EPINEPHRINE and antihistamine administered by injection, which immediately and effectively stop the progression of the hypersensitivity reaction. When airway (bronchial) symptoms are severe, the doctor may also administer an injectable corticosteroid medication. Swelling and related symptoms usually abate within a few minutes. Supportive treatment for symptoms often includes OXYGEN THERAPY and intravenous fluids. Most people completely recover within a few hours.

Bee stings, peanuts, intravenous penicillin, and intravenous contrast dyes for radiology procedures are the most common allergens responsible for anaphylaxis. However, anaphylaxis is possible with any ALLERGY. Anaphylaxis is fatal for about 200 Americans each year. Some people may benefit from DESENSITIZATION, depending on the allergen responsible for the hypersensitivity reaction, to mitigate the IMMUNE RESPONSE with future exposures. People who know they have severe allergies may get a doctor's prescription for an anaphylaxis

kit, which contains a prefilled syringe of injectable epinephrine.

See also BRONCHUS-ASSOCIATED LYMPHOID TISSUE (BALT); MAST CELL.

angioedema A HYPERSENSITIVITY REACTION (allergic reaction) that produces swelling and fluid accumulation beneath the surface of the SKIN, similar in appearance to URTICARIA (hives). Angioedema occurs in response to HISTAMINE release and typically affects the face, especially around the eyes and lips, and can be life threatening when it is severe or if it develops in the throat. Swelling in the form of welts may also occur on the hands and feet. Hypersensitivity reaction to ingested allergens is the most common cause of angioedema.

Difficulty BREATHING with angioedema is a medical emergency that requires immediate hospital care.

The doctor can diagnose angioedema based on the appearance of the symptoms and the person's exposure to an ALLERGEN. Treatment may include ANTIHISTAMINE MEDICATIONS; CORTICOSTEROID MEDICATIONS; or for severe symptoms, an EPINEPHRINE injection. Cool cloths applied to the sites of the angioedema may further ease discomfort. After the histamine release ends, the body reabsorbs the fluid. Relief improves as the swelling goes down, and symptoms are generally gone within three or four days. Avoiding the allergen prevents the hypersensitivity reaction and the resulting angioedema.

There is a form of angioedema, hereditary angioedema, that is an inherited genetic disorder and not a hypersensitivity reaction. Though there is similar swelling beneath the skin, there is no histamine release.

See also ANAPHYLAXIS; GENETIC DISORDERS; IMMUNE RESPONSE; LIVING WITH ALLERGIES.

antibody A unique molecule that binds with a specific ANTIGEN so the IMMUNE SYSTEM can neutralize or destroy the antigen. Antigens are molecular markers on the surfaces of cells that identify the cells to the immune system. Antibodies are the immune system's infantry, patrolling the BLOOD and LYMPH circulations and responding to fight INFECTION when invading pathogens breach the barriers intended to keep them out of the body. Every time the immune system encounters new antigens it crafts new antibodies—a distinct and unique antibody for each antigen. Though antibodies all derive from IMMUNOGLOBULIN E (IgE), each kind of antibody binds only with its specific antigen. The immune system has the capacity to produce millions of unique antibodies.

B-cell lymphocytes, a type of white blood cell (LEUKOCYTE), produce antibodies each time the immune response presents a foreign antigen. Once sensitized to a specific antigen and programmed to produce antibodies for it, the B-CELL LYMPHOCYTE becomes a plasma cell and circulates in the blood and lymph. Whenever the plasma cell encounters its antigen, it churns out antibodies and releases them into the blood and lymph. Thousands to millions of plasma cells are present in the body for each antibody the immune response generates.

The antibody response is the foundation of ANTIBODY-MEDIATED IMMUNITY, also called humoral immunity, the process by which the immune system prevents reinfection by specific pathogens. Vaccines manipulate antibody-mediated immunity by introducing weakened pathogens (such as viruses and BACTERIA) to stimulate B-cell lymphocytes to produce antibodies against them. The blood and lymph circulations then contain the antibodies though the person has never had the infection.

Blood tests for the presence of specific antibodies help doctors diagnose numerous health conditions and determine whether a person has immunity against viral infections such as RUBELLA (German measles) and infectious mononucleosis. Antibody testing is also a key step in determining the match potential between an organ transplant recipient and the donor organ.

For further discussion of antibodies within the context of the structures and functions of the immune system, please see the overview section "The Immune System and Allergies."

See also ALLERGY; CELL-MEDIATED IMMUNITY; CELL STRUCTURE AND FUNCTION; COMPLEMENT CASCADE; GAMMAGLOBULIN; HYPERSENSITIVITY REACTION; MONOCLONAL ANTIBODIES (MABS); MONONUCLEOSIS, INFECTIOUS; ORGAN TRANSPLANTATION; PATHOGEN; VACCINE; VIRUS.

antibody-mediated immunity The mechanism through which specialized immune cells, primarily B-cell lymphocytes, carry out the IMMUNE RESPONSE to protect the body from extracellular pathogens (disease-causing entities, such as BACTERIA and other microbes, present in the BLOOD or LYMPH that have not invaded the body's cells). Antibody-mediated immunity, also called humoral immunity, encompasses the functions of ANTIBODY production and immune memory. Antibody-mediated immunity functions collaboratively with CELL-MEDIATED IMMUNITY to help protect the body from INFECTION.

Specialized B-cell lymphocytes called PLASMA cells produce antibodies, protein molecules that circulate in the blood and lymph. Exposure to antigens for which they are sensitized activates plasma cells to produce antibodies. The antibodies bind with the antigens that match their ANTIGEN receptors (molecular sites that match the configuration of the antigen). The antibody–antigen bond activates the COMPLEMENT CASCADE, a complex interaction of blood proteins (the complement system) that results in penetration and death of the foreign cell.

Antibody binding also releases various CYTOKINES (protein molecules that serve as chemical messengers) that then activate other processes in the immune response. Immune cells that may respond to these messages include macrophages, granulocytes (basophils, eosinophils, and neutrophils), and T-cell lymphocytes (notably helper T-cells [Th2 cells]). The sequence of events takes about 36 hours to unfold after the IMMUNE SYSTEM recognizes the antigen as foreign. The immune response then works to neutralize the threat.

Memory B-cells circulate in the blood and lymph for an extended period of time. They hold a "memory" imprint of specific pathogens. When the PATHOGEN again enters the body, the memory-B cells remember and immediately ramp up antibody production. This process shortcuts the usual immune response, allowing the immune system to mount a defense before the pathogen can initiate an infection.

See also B-CELL LYMPHOCYTE; CELL STRUCTURE AND FUNCTION; GRANULOCYTE; MACROPHAGE; T-CELL LYMPHOCYTE; VACCINE.

antigen A molecule that resides on the surface of a cell membrane and is capable of stimulating an IMMUNE RESPONSE. Antigen molecules are either lipoproteins (lipid and protein) or glycolipids (lipid and GLUCOSE). Each cell has numerous antigens that that identify it to the IMMUNE SYSTEM. Cells that belong to the body bear antigens that mark them as self cells; the immune system does not react to them. The antigens on cells that are foreign to the body alert the immune system to the presence of nonself cells, which activates an immune response. Foreign or nonself antigens cause the immune system to develop antibodies, unique proteins (immunoglobulins) that inactivate or destroy specific antigens.

ANTIGENS AND BLOOD TYPE

Antigens form the basis of the ABO and rhesus (Rh factor) classification for BLOOD TYPE. Antigens coat the cell membrane surface of erythrocytes (red BLOOD cells) for blood types A, B, and AB. The erythrocytes of type O blood do not have antigens. Erythrocytes may also have Rh antigens, designated as "positive" when used to identify blood type. For example, A+ erythrocytes bear type A and Rh antigens. O– erythrocytes have neither ABO antigens nor Rh antigens.

Antigen Processing

Macrophages, tissue-bound phagocytic white BLOOD cells that start life as monocytes circulating in the blood, are abundant in the LYMPH tissues. They are the immune cells that sound the alarm to the rest of the immune system that nonself antigens are present. When a macrophage encounters a foreign entity, it surrounds and ingests it. As the MACROPHAGE consumes the invader, it displays the invader's antigens on the surface of its cell membrane. This display announces the presence of the antigens to other immune cells, notably T-cell lymphocytes, which then mount a full immune response. Other cells that may serve as antigen-presenting cells include B-cell lymphocytes and dendritic cells. Once T-cell lymphocytes "read" the antigen message the macrophage displays, they respond by attacking and killing the invader. Correspondingly, B-cell

lymphocytes (PLASMA cells) generate antibodies to further target the antigen.

Antigens and Cancer

The antigens on the surface of cancer cells have become a focus of much research into early diagnosis and new treatments for cancer. Cancer cells begin as normal cells in the body, bearing self-cell antigens. As the cells change and become cancerous they develop additional antigens. Blood tests can detect some of these antigens, such as PROSTATE SPECIFIC ANTIGEN (PSA) on PROSTATE CANCER cells. Cancer researchers believe the immune response fails to recognize the mixed antigen population on cancer cells as nonself, which allows the cancer to grow.

For further discussion of antigens within the context of the structures and functions of the immune system, please see the overview section "The Immune System and Allergies."

See also ANTIBODY; B-CELL LYMPHOCYTE; BLOOD TRANSFUSION; CELL STRUCTURE AND FUNCTION; CLUSTERS OF DIFFERENTIATION; COMPLEMENT CASCADE; CYTOKINES; ERYTHROCYTE; HUMAN LEUKOCYTE ANTIGENS (HLAS); IMMUNOGLOBULIN; IMMUNOTHERAPY; MONOCYTE; TUMOR MARKERS.

antihistamine medications Medications that block the action of HISTAMINE, a chemical that acts on the BLOOD vessels during an IMMUNE RESPONSE to allow fluid to flood the tissues. The resulting INFLAMMATION is part of the body's means of delivering INFECTION-fighting agents to the site (such as T-lymphocytes, CYTOKINES, and antibodies). However, this response is exaggerated in a HYPERSENSITIVITY REACTION, during which histamine secretion is excessive or continues after the immune response has neutralized the triggering ANTIGEN.

Large, granulated leukocytes (white blood cells) called mast cells produce, store, and release histamine (as well as serotonin and other chemicals). Mast cells reside in the mucous membranes of the respiratory tract (nasal passages, nasal sinuses, TRACHEA, and bronchi) and the gastrointestinal tract (primarily the STOMACH). Mast cells also store and release serotonin. Histamine is primarily responsible for the inflammatory changes that result in hypersensitivity reaction (allergic reaction).

STABILIZING MAST CELLS TO PREVENT HISTAMINE RELEASE

A different therapeutic approach to managing the HISTAMINE cascade in HYPERSENSITIVITY REACTION is to regulate histamine release at the level of the mast cells, which is most effective as a treatment for ALLERGIC ASTHMA (hypersensitivity reaction of the airways). Drugs called MAST-CELL stabilizers work by preventing the granules in mast cells from releasing histamine (called degranulation) as part of the IMMUNE RESPONSE. Mast-cell stabilizers to treat allergic ASTHMA include cromolyn and nedocromil.

How These Medications Work

Antihistamines work by blocking the ability of histamine to bind with histamine receptors on the surfaces of cell membranes. Antihistamines target the two types of histamine receptors involved with the immune response: H1 and H3. H1 receptors regulate arteriole dilation and capillary permeability. Histamine causes dilation of the arterioles, the body's tiniest arteries, to increase blood flow to the tissues and increases the flow of plasma out from the capillaries into the interstitial spaces, to flood the tissues with antibodies, cytokines, PROSTAGLANDINS, and other molecules essential to the immune response.

When taken at the onset of symptoms (while histamine release is still taking place) or prophylactically (to prevent histamine release, such as to treat seasonal allergies), antihistamine medications relieve the common symptoms of ALLERGY such as itching and sneezing. However, antihistamines cannot reverse the effects of histamine release after they occur or reduce inflammation that has already developed. Antihistamine medications to treat hypersensitivity reaction are available in oral, topical, inhalation, and injection preparations. Doctors may also prescribe antihistamines to relieve NAUSEA, particularly that of motion sickness, and mild anxiety.

First-generation antihistamines, long the mainstay of treatment for allergies, are nonselective. They block both H1 and H3 receptors. H1 blocking subdues symptoms of hypersensitivity reaction. H3 receptors signal BRAIN neurotransmitters in the HYPOTHALAMUS that regulate alertness and the nau-

sea center. Antihistamine medications with H3 blocking capability thus cause drowsiness and relieve nausea as well. Second-generation antihistamine medications are selective. They block primarily H1 receptors and have little effect on H3 receptors; thus they do not generally cause drowsiness and provide little or no relief of nausea. Third-generation antihistamine medications derive from second-generation antihistamines and are purported to have fewer side effects and adverse reactions though functionally are no different. Many antihistamine medications are available in the United States as OVER-THE-COUNTER (OTC) DRUGS, sometimes in combination with a decongestant or other ingredients. Manufacturers often market OTC antihistamines as allergy-relief products. Other antihistamines require a doctor's prescription.

ANTIHISTAMINE MEDICATIONS

First-Generation (Nonselective) Antihistamines	
brompheniramine	chlorpheniramine
dexchlorpheniramine	dimenhydrinate
diphenhydramine	doxylamine
hydroxyzine	phenindamine
pheniramine	pyrilamine
triprolidine	
Second-Generation (Selective H1) Antihistamines	
acrivastine	azatadine
cetirizine	clemastine
cyproheptadine	loratadine
mizolastine	
Third-Generation (Selective H1) Antihistamines	
desloratadine	fexofenadine
levocetirizine	

Therapeutic Applications

Doctors prescribe or recommend antihistamine medications to treat ALLERGIC RHINITIS, ALLERGIC CONJUNCTIVITIS, and ALLERGIC DERMATITIS. Most of the nonselective antihistamines cause significant drowsiness; doctors prescribe or recommend them for intermittent insomnia (difficulty sleeping). Meclizine is an H3 receptor antihistamine effective for nausea and VOMITING, especially that associated with motion sickness. Meclizine has little effect on H1 receptors, however, so does not influence the immune response or relieve symptoms of hypersensitivity reaction.

Some antihistamine medications have other therapeutic applications, such as

- anxiety: hydroxyzine
- sedative and sleep aid: diphenhydramine, doxylamine, hydroxyzine
- nausea and vomiting: dimenhydrinate, diphenhydramine, hydroxyzine
- VERTIGO: dimenhydrinate, diphenhydramine
- early PARKINSON'S DISEASE: diphenhydramine

Risks and Side Effects

In general antihistamine medications cause few side effects other than drowsiness, although can raise BLOOD PRESSURE. People who take other medications to treat chronic health conditions should check with their doctors before taking antihistamines, as antihistamines can exacerbate symptoms or interfere with the actions of other drugs.

See also ANTIBODY; ARTERY; CORTICOSTEROID MEDICATIONS; CAPILLARY BEDS; GENERALIZED ANXIETY DISORDER (GAD); H2 ANTAGONIST (BLOCKER) MEDICATIONS; LIVING WITH ALLERGIES; LYMPHOCYTE; NEUROTRANSMITTER; PROTON PUMP INHIBITOR MEDICATIONS; SNEEZE.

antimitochondrial antibodies Autoantibodies the IMMUNE SYSTEM produces that attack the mitochondria within self cells. Mitochondria are the organelles (functional structures) within a cell that generate the energy the cell needs to carry out its activities. Antimitochondrial antibodies are proteins that bind with antigens (other proteins) on the inner walls of the mitochondria, blocking the ability of the mitochondria to convert oxygen to energy. The cell dies as a result.

CONDITIONS IN WHICH ANTIMITOCHONDRIAL ANTIBODIES ARE PRESENT

CIRRHOSIS	PRIMARY BILIARY CIRRHOSIS
PRIMARY SCLEROSING CHOLANGITIS	RHEUMATOID ARTHRITIS
SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)	THYROIDITIS

A BLOOD test called the antimitochondrial ANTIBODY (AMA) titer detects and measures antimitochondrial antibodies in the blood circulation. Their presence indicates various AUTOIMMUNE DISORDERS, notably PRIMARY BILIARY CIRRHOSIS and PRIMARY SCLE-

ROSING CHOLANGITIS, two conditions that damage the LIVER. Normally antimitochondrial antibodies are not present.

See also ANTIGEN; CELL STRUCTURE AND FUNCTION; IMMUNE RESPONSE.

antiphospholipid antibodies Autoantibodies the IMMUNE SYSTEM produces that attack phospholipids, fatty substances in the cell membranes of BLOOD cells and connective tissue cells. Antiphospholipid antibodies interfere with blood clotting (COAGULATION) and are present in a number of AUTOIMMUNE DISORDERS that affect connective tissue, such as RHEUMATOID ARTHRITIS (affecting the joints) and VASCULITIS (affecting the blood vessels). Antiphospholipid antibodies are also present in SYSTEMIC LUPUS ERYTHEMATOSUS (SLE).

Several blood tests can detect and measure the level of antiphospholipid antibodies, reported as a titer. Antiphospholipid antibodies are not normally present. Positive findings when there are no other autoimmune conditions may indicate a diagnosis of primary antiphospholipid syndrome. The primary effect of antiphospholipid antibodies is increased blood clotting, resulting in conditions such as DEEP VEIN THROMBOSIS (DVT), TRANSIENT ISCHEMIC ATTACK (TIA), repeated miscarriage in PREGNANCY, HEART ATTACK, and STROKE.

See also ANTIBODY; ANTIGEN; ANTIMITOCHONDRIAL ANTIBODIES.

atopy A genetically predisposed HYPERSENSITIVITY REACTION. Atopy is typically chronic. The most common forms of atopy are

- atopic ASTHMA, which affects the airways (bronchi)
- atopic DERMATITIS, which affects the SKIN
- atopic rhinitis, which affects the nasal passages (nose)
- atopic CONJUNCTIVITIS, which affects the membranes that line the eyelids (conjunctiva) and the sclera (white) of the EYE

The symptoms of atopic conditions are the classic symptoms of ALLERGY, though tend to appear at the slightest exposure to allergens and linger for an extended time. Atopy is a type I or IMMUNOGLOBULIN E (IgE) hypersensitivity reaction that occurs fairly immediately after exposure to the ALLERGEN. Treatments for atopic conditions target the IMMUNE RESPONSE as well as symptom relief and may include oral and topical ANTIHISTAMINE MEDICATIONS and CORTICOSTEROID MEDICATIONS. Avoiding known or suspected allergens significantly reduces the severity of an atopic attack.

See also ALLERGIC ASTHMA; ALLERGIC CONJUNCTIVITIS; ALLERGIC DERMATITIS; ALLERGIC RHINITIS; BRONCHUS; GENETIC PREDISPOSITION; LIVING WITH ALLERGIES.

autoimmune disorders Health conditions in which the body's IMMUNE RESPONSE loses the ability to identify certain self cells and attacks them. Autoimmune disorders may produce symptoms that are localized (affect a clearly defined part of the body), systemic (affect a body system), or generalized (affect the body as a whole or across several systems). Though researchers do not know what causes the immune response to lose tolerance for certain antigens, causing it to identify self cells as nonself cells, they do know that a person who has one autoimmune disorder is at risk for developing others.

AUTOIMMUNE DISORDERS

autoimmune HEPATITIS	BULLOUS PEMPHIGOID
dermatomyositis	DIABETES (type 1)
DISCOID LUPUS ERYTHEMATOSUS (DLE)	GOODPASTURE'S SYNDROME
GRAVES'S DISEASE	Hashimoto's THYROIDITIS
INFLAMMATORY BOWEL DISEASE (IBD)	MULTIPLE SCLEROSIS
MYASTHENIA GRAVIS	PEMPHIGUS
pernicious ANEMIA	POLYMYOSITIS
REITER'S SYNDROME	RHEUMATOID ARTHRITIS
scleroderma	SJÖGREN'S SYNDROME
SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)	VASCULITIS

Over time the immune attacks permanently damage or destroy tissue. Autoimmune disorders are chronic; though treatment may control symptoms, it does not cure the disorder. Symptoms and outlook vary with the autoimmune disorder. Some autoimmune disorders, such as type 1 DIABETES and GRAVES'S DISEASE, are life threatening without treatment. Treatment is generally IMMUNOSUPPRESSIVE THERAPY with IMMUNOSUPPRESSIVE MEDICATIONS that block certain aspects of the immune response. Further treatment may be necessary to counter the damage the autoimmune

disorder causes, such as INSULIN therapy for diabetes. The course of disease may be unpredictable. Though autoimmune disorders tend to gradually worsen over time, many remain manageable with minimal symptoms or disruption of activities. There are no known preventive measures.

See also COMMON VARIABLE IMMUNE DEFICIENCY (CVID); COMPLEMENT CASCADE; DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (DMARDS); HIV/AIDS; LIVING WITH IMMUNE DISORDERS; MULTIPLE CHEMICAL SENSITIVITY SYNDROME; PARTIAL COMBINED IMMUNODEFICIENCY (PCID).

B

B-cell lymphocyte A type of white BLOOD cell (LEUKOCYTE) responsible for ANTIBODY-MEDIATED IMMUNITY (also called humoral immunity). B-cell lymphocytes are so named because they come to maturity in the BONE MARROW (in contrast to T-cell lymphocytes, which come to maturity in the THYMUS). B-cell lymphocytes produce antibodies in reaction to the presence of antigens. The bone marrow generates millions of B-cell lymphocytes each day. Each B-cell lymphocyte is specific for a unique ANTIGEN.

B-cell lymphocytes may be memory B-cells, which "remember" specific antigens to mobilize a rapid IMMUNE RESPONSE upon detecting their presence, and PLASMA cells, which produce antibodies.

- Plasma cells generate antibodies in response to the presence of antigens.
- Memory B-cells remain in the circulation of the blood and LYMPH, carrying inactive antibodies. Each memory B-cell has antibodies specific to a particular antigen the immune response has previously encountered. When the memory B-cell encounters the antigen again, it immediately begins producing antibodies.

Health conditions that affect B-cell lymphocytes include cancers, such as certain types of LEUKEMIA and lymphoma, and acquired immune and AUTOIMMUNE DISORDERS.

For further discussion of B-cell lymphocytes within the context of the structures and functions of the immune system, please see the overview section "The Immune System and Allergies."

See also CELL-MEDIATED IMMUNITY; HIV/AIDS; T-CELL LYMPHOCYTE.

biological response modifier See IMMUNOTHERAPY.

bronchus-associated lymphoid tissue (BALT) Loosely organized clusters of LYMPH tissue beneath the epithelium (tissue that forms the mucous lining) of the bronchi (inner airways) in the LUNGS. These clusters of lymph tissue have preventive, protective, and cleanup responsibilities within the IMMUNE RESPONSE. They contain

- macrophages and dendritic cells, which are phagocytic cells that consume the debris of pathogens other leukocytes (white BLOOD cells) kill
- T-cell lymphocytes, which destroy PATHOGEN-bearing cells
- B-cell lymphocytes, which produce the ANTIBODY IMMUNOGLOBULIN A (IgA), that helps keep BACTERIA and viruses from adhering to mucous tissues, such as the lining of the nasal sinuses and the bronchi
- M cells (folded, M-shaped cells that engulf pathogens and transport them to phagocytes), which participate in the various stages of ANTIGEN dispensation

BALT, like collections of accessory lymphoid tissue elsewhere in the body, reinforces the presence of the IMMUNE SYSTEM in areas where the body is vulnerable to invasion of pathogens (viruses, bacteria, and other potentially harmful substances). A specific role of BALT is to provide an extra layer of immune protection to block or limit access by viruses that cause infections specific to the lungs, such as INFLUENZA and PNEUMONIA.

For further discussion of BALT within the context of the structures and functions of the immune system, please see the overview section "The Immune System and Allergies."

See also BRONCHUS; CELL STRUCTURE AND FUNCTION; GUT-ASSOCIATED LYMPHOID TISSUE (GALT); LEUKOCYTE; LYMPHOCYTE; MACROPHAGE; MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT); NOSE-ASSOCIATED LYMPHOID TISSUE (NALT); PHAGOCYTE; PHAGOCYTOSIS; SKIN-ASSOCIATED LYMPHOID TISSUE (SALT); VIRUS.

C

cell-mediated immunity The protective mechanism through which specialized immune cells, primarily T-cell lymphocytes and natural killer (NK) cells, carry out the IMMUNE RESPONSE to protect the body from intracellular pathogens (disease-causing entities, such as viruses and parasites, that invade the body's cells). Cell-mediated immunity encompasses cytotoxic (death of invading cells) and phagocytic (consumption of cellular debris) activities. Cell-mediated immunity functions collaboratively with ANTIBODY-MEDIATED IMMUNITY to protect the body from INFECTION.

Several kinds of T-cell lymphocytes participate in cell-mediated immunity. They include

- cytotoxic T-cells, which respond directly to antigens for which they are sensitized and kill the cells that bear them
- helper T-cells (Th1 cells), also called CD-4 cells, which release CHEMOKINES in response to the presence of the antigen-bearing cells
- memory T-cells, which are essential for long-term immunity against infections such as MEASLES and POLIOMYELITIS (activated through disease or vaccination)
- suppressor T-cells, which bring the immune response to a close when the threat is gone

Macrophages set cell-mediated immunity in action when they display the antigens of a consumed cell. When these are nonself antigens, cytotoxic T-cells respond to kill other cells bearing the ANTIGEN. When the antigen is one the body has previously encountered, memory T-cells sensitized to the particular antigen rapidly convert to cytotoxic T-cells and mount a fast-strike immune response. The ability of cell-mediated immunity to rid the body of nonself-antigen-bearing cells is highly effective for controlling infection though also becomes problematic in ORGAN TRANSPLANTATION. Cell-mediated immunity, with its focus on nonself antigens, is key to GRAFT VS. HOST DISEASE and organ transplant rejection.

The NK cell, a type of granular LEUKOCYTE, does not respond to antigens. Rather, it responds to MAJOR HISTOCOMPATIBILITY COMPLEX (MHC) molecules on the surfaces of cell membranes. Attacking NK cells produce CYTOKINES that weaken the cell membrane of the targeted cells, which indirectly causes the death of the cells. NK cells also respond to tumor antigens and are particularly active in killing cancer cells. Researchers believe NK cells have a limited ability to recognize changes in cells that alter cellular identity (altered self), such as those occurring when cells turn cancerous. However, researchers do not understand the mechanisms of this recognition or to what extent NK cells are able to suppress the growth of cancer cells.

See also HYPERSENSITIVITY REACTION; MACROPHAGE; MONONUCLEAR PHAGOCYTE SYSTEM; NATURAL KILLER (NK) CELL; PARASITE; PATHOGEN; PHAGOCYTE; PHAGOCYTOSIS; T-CELL LYMPHOCYTE; VACCINE; VIRUS.

chemokines Proteins, also called chemotactic CYTOKINES, that draw or direct leukocytes to the scene of INFECTION within the body. Macrophages produce chemokines when they encounter foreign cells, instigating an IMMUNE RESPONSE. Some chemokines act as homing signals, marking the foreign cells so responding immune cells can zero in on them. Other chemokines send out biochemical "alerts" that attract circulating monocytes and lymphocytes.

Chemokines are integral in the process of angiogenesis (the development and growth of

new BLOOD vessels) that occurs when both HEALING and tumor progression (such as in cancer) takes place. Researchers are exploring ways to target chemokines as a means of shutting down angiogenesis, which has the potential to starve tumors.

See also IMMUNOTHERAPY; LEUKOCYTE; LYMPHOCYTE; MACROPHAGE; TUMOR NECROSIS FACTORS (TNFS).

clusters of differentiation A system of classifying lymphocytes according to the collections of antigens on the surface of their cell membranes, also called CD markers. Each CD has a specific role in cell signaling and communication, guiding cell function and response. CDs are critical to the normal function of the IMMUNE SYSTEM. Some of the major CDs are

- CD-1, which populates B-cell lymphocytes and macrophages and has a role in ANTIGEN presentation
- CD-2, which populates T-cell lymphocytes and natural killer (NK) cells and activates T-cells
- CD-3, which populates T-cell lymphocytes and facilitates antigen binding (the ability of T-cell lymphocytes to receive biochemical messages)
- CD-4, which populates T-helper cells (T-cell lymphocytes that direct IMMUNE RESPONSE to INFECTION) and is a key marker for monitoring the progression of HIV/AIDS
- CD-5, which populates B-cell lymphocytes that produce IMMUNOGLOBULIN M (IgM)
- CD-7, which populates T-cell lymphocytes in acute lymphocytic LEUKEMIA (ALL) and is a marker for STEM CELL leukemias
- CD-8, which populates T-suppressor cells (T-cell lymphocytes that end the immune response) and is a key marker for monitoring the progression of HIV/AIDS

CD-4 AND HIV/AIDS

CD-4 has become an important marker in tracking the progression of HIV/AIDS, as HIV-1 and HIV-2 bind with this ANTIGEN to gain access to the body. CD-4 receptors are abundant on certain T-cell lymphocytes called T-helper cells (also called T_4 cells). In health, CD-4 coordinates numerous aspects of the IMMUNE RESPONSE. When pathogens such as HIV bond with CD-4 receptors, they block the ability of CD-4 to signal other immune cells. This communication failure disrupts the IMMUNE SYSTEM's ability to mount an effective immune response. HIV also uses the T-helper cells to replicate itself, further spreading INFECTION. In combination, these events allow OPPORTUNISTIC INFECTION that can overwhelm the body.

See also ANTIBODY; CYTOKINES; HUMAN LEUKOCYTE ANTIGENS (HLAS); B-CELL LYMPHOCYTE; LYMPHOCYTE; MACROPHAGE; MAJOR HISTOCOMPATABILITY COMPLEX (MHC); MONOCLONAL ANTIBODIES (MABS); NATURAL KILLER (NK) CELL; PHENOTYPE; T-CELL LYMPHOCYTE.

colony-stimulating factors (CSFs) Molecules that stimulate the growth of leukocytes (white BLOOD cells) in the BONE MARROW. The body produces minute quantities of CSFs to regulate LEUKOCYTE production, maintaining the various types of leukocytes at appropriate levels to meet the needs of immune function. CSF production increases during INFECTION and other demands for higher quantities of white blood cells.

In the 1990s researchers isolated the genes that encode CSFs, permitting the use of recombinant technology to create synthetic versions of CSFs for therapeutic applications. Today doctors administer CSFs to rapidly restore white blood cell production after IMMUNOABLATION during the course of treatment for some forms of LEUKEMIA and certain other cancers for which BONE MARROW TRANSPLANTATION is a treatment option, and some chemotherapeutic regimens that are known to be very ablative to the white blood cells. Immunoablation uses high-DOSE CHEMOTHERAPY or RADIATION THERAPY to destroy the diseased bone marrow. During the approximately six weeks it takes for the transplanted bone marrow to begin producing new blood cells, the person has no immune function and is extremely vulnerable to infection. CSF therapy dramatically shortens this period of vulnerability, stimulating leukocyte production within days of the bone marrow transplantation.

See also CYTOKINES; GENE; HEMATOPOIESIS; IMMUNE RESPONSE; IMMUNOSUPPRESSIVE THERAPY; RECOMBINANT DNA.

common variable immunodeficiency (CVID) An immune disorder in which the IMMUNE SYSTEM lacks the ability to produce adequate antibodies to protect the body from INFECTION. Though there are normal numbers of B-lymphocytes in the BLOOD circulation, these ANTIBODY-producing cells are lacking IMMUNOGLOBULIN G (IgG), a protein essential for ANTIGEN recognition and antibody production. IgG is the foundation for most antibodies that the immune system produces.

Symptoms and Diagnostic Path

Symptoms of CVID can show up any time after about age 10 though most commonly appear in the late 20s and early 30s. Generally the person has the same type of infection repeatedly, as the immune system is not producing antibodies to protect against the infectious agent. The key symptom is a progressive pattern of recurrent or chronic infections. Infections are most commonly upper respiratory, SINUSES, THROAT, and middle EAR—typically BRONCHITIS, PNEUMONIA, PHARYNGITIS, SINUSITIS, and OTITIS media. Infections may be viral, bacterial, fungal, or parasitic. Some people also have gastrointestinal infections. The severity of infection varies among people who have CVID as well as within an individual from infection to infection. The diagnostic path includes blood tests to measure IgG and antibody levels. Immunoglobulin A (IgA) and immunoglobulin M (IgM) levels may also be low.

Treatment Options and Outlook

The main therapeutic course is reducing exposure to known infection (such as common viral infections) and treatment with ANTIBIOTIC MEDICATIONS at the first sign of infection. GAMMAGLOBULIN injections can bolster the immune system, though the gammaglobulin (which comes from blood or PLASMA donors) may not contain the specific antibodies the person needs. With effective medical management and diligent prevention efforts, most people who have CVID can enjoy relatively normal lifestyles and life expectancy.

Risk Factors and Preventive Measures

Most CVID is acquired, though researchers do not know what causes it to occur. There are no known measures for preventing CVID. CVID occurs more frequently in people who have AUTOIMMUNE DISORDERS such as RHEUMATOID ARTHRITIS or SYSTEMIC LUPUS ERYTHEMATOSUS (SLE). Prompt diagnosis and appropriate treatment are essential for preventing substantial lung damage that can occur from recurrent infections.

See also BACTERIA; FUNGUS; HAND WASHING; LUNGS; PARTIAL COMBINED IMMUNODEFICIENCY (PCID); PARASITE; PERSONAL HYGIENE; SEVERE COMBINED IMMUNODEFICIENCY (SCID); LIVING WITH IMMUNE DISORDERS; VIRUS.

complement cascade The series of events that take place when an ANTIBODY binds with an ANTIGEN, activating the complements. Complements are proteins that participate in immune and inflammatory processes, acting primarily to kill antibody-marked cells. The biochemical interactions that take place with their activation ultimately lead to the formation of a protein structure called the terminal complement component or the membrane attack complex. The membrane attack complex penetrates the cell membrane of the antibody-marked cell. This penetration kills the cell and coats it in proteins that mark it for PHAGOCYTOSIS, the process through which LEUKOCYTE (white BLOOD cell) scavenger cells, called phagocytes, consume the debris that remains after the attacked cell dies.

There are about 30 complement proteins, also called complement factors, in the blood circulation. They remain inactive until antibody–antigen bindings or certain other immune responses activate them. Doctors classify activated complements into nine major molecular complexes identified as C1–C9. C1–C4 form the preliminary pathways leading to the formation of the membrane attack complex. C5–C9 collectively form the membrane attack complex. Other proteins interact with the complements to keep their actions in check. Disintegration of the complement complexes begins immediately after their activation to prevent them from damaging other cells.

Blood tests can measure complement activity in the body. Complement activity is often increased in the presence of cancer and decreased with certain AUTOIMMUNE DISORDERS such as SYSTEMIC LUPUS ERYTHEMATOSUS (SLE). Complement activity also diminishes in GRAFT VS. HOST DISEASE.

Deficiencies in various complement complexes increase susceptibility to INFECTION and the risk for disorders of the immune system. People who have deficiencies in the preliminary complement cascade pathways that unfold before the formation of the membrane attack complex are particularly vulnerable to infections such as MENINGITIS and PNEUMONIA. Certain of the pathogens that can cause these infections are encapsulated—viruses and BACTERIA that enclose themselves in capsules, or envelopes. The purpose of this encapsulation is to protect the pathogen against the body's defense mechanisms. When defects weaken those mechanisms, the pathogens gain advantage in establishing themselves—and infection—within the body.

Other complement deficiencies are common in SLE and some forms of VASCULITIS (disorders involving autoimmune INFLAMMATION of blood vessels). Treatment focuses on the symptoms of the consequential disorders, notably aggressive antibiotic therapy for infection. There are, as yet, no treatments to correct complement deficiencies. Doctors recommend meningococcal, pneumococcal, and *Haemophilus influenzae* VIRUS vaccinations for people who have complement deficiencies, to bolster the IMMUNE SYSTEM's ability to protect against infections from these pathogens.

For further discussion of the complement cascade within the context of the structures and functions of the immune system, please see the overview section "The Immune System and Allergies."

See also ANTIBIOTIC MEDICATIONS; IMMUNE RESPONSE; MONONUCLEAR PHAGOCYTE SYSTEM; ORGAN TRANSPLANTATION; PHAGOCYTE; VACCINE.

corticosteroid medications Anti-inflammatory medications that suppress INFLAMMATION and other aspects of the IMMUNE RESPONSE. Corticosteroid medications are synthetic variations of the body's natural HORMONE CORTISOL, which the ADRENAL GLANDS produce. Corticosteroids come in injectable, oral, inhalant, and topical preparations.

How These Medications Work

Corticosteroid medications work by blocking a number of the pathways in the immune response, key among them those that produce inflammation. They suppress the COMPLEMENT CASCADE, activation of antibodies, and production of eosinophils (white BLOOD cells that become abundant in a HYPERSENSITIVITY REACTION). Eosinophils are also important for fighting INFECTION, so suppressing them reduces the IMMUNE SYSTEM's ability to mount an effective defense when infection occurs. Corticosteroids also act to suppress MAST CELL release of HISTAMINE, LEUKOTRIENES, and PROSTAGLANDINS—biochemicals that facilitate inflammation.

There are three general types of corticosteroids, classified according to how they act in the body: glucocorticoids, mineralocorticoids, and ANDROGENS (the sex hormones). Glucocorticoids have the strongest anti-inflammatory action; most corticosteroid drugs are either glucocorticoids or a combination of glucocorticoid and mineralocorticoid. ALDOSTERONE, another hormone the adrenal cortex produces, is a mineralocorticoid used therapeutically as hormone replacement to treat ADDISON'S DISEASE (a condition in which the adrenal glands fail). However, aldosterone and other mineralocorticoids alone have very little anti-inflammatory action.

CORTICOSTEROID MEDICATIONS

betamethasone	cortisone
desoximometasone	fluticasone
dexamethasone	hydrocortisone
methylprednisolone	mometasone
prednisolone	prednisone
triamcinolone	

Therapeutic Applications

Doctors may prescribe corticosteroid medications to relieve symptoms of moderate to severe hypersensitivity reaction, to prevent GRAFT VS. HOST DISEASE in bone marrow transplant recipients, and to treat chronic inflammatory conditions such as severe OSTEOARTHRITIS, RHEUMATOID ARTHRITIS, ANKYLOSING SPONDYLITIS, PSORIASIS, SYSTEMIC LUPUS ERYTHEMATOSUS (SLE), and INFLAMMATORY BOWEL DISEASE (IBD). Corticosteroids in nasal sprays and inhalant forms are effective treatments for ALLERGIC RHINITIS and ALLERGIC ASTHMA. Systemic corticosteroid medications are also among the treatment options for severe asthma and certain other chronic inflammatory lung conditions.

It is important to take or use corticosteroid products correctly, particularly inhalants and nasal

sprays. Generally, corticosteroids are most effective when taken on a regular schedule to prevent the inflammatory process from developing, though they also can help suppress an inflammatory response after it begins. Because long-term corticosteroid therapy also suppresses the function of the adrenal glands, the body stops producing cortisol and becomes dependent on the external source of corticosteroids (the medication). It is important to reduce the dose over time (taper) when stopping a systemic corticosteroid, to allow the adrenal glands to resume cortisol production. Suddenly stopping systemic corticosteroid therapy can result in a rebound syndrome, with symptoms of inflammation, PAIN, and FEVER.

Risks and Side Effects

Side effects are uncommon with short-term systemic (oral and injection forms), inhalation, or topical corticosteroid use. However, corticosteroids tend to be less effective with repeated or chronic use. Injected corticosteroids, such as to treat inflammation in joints, can cause tissue damage over time. Doctors generally limit corticosteroid injections to prevent such damage. Long-term use of inhaled corticosteroids is often irritating to the tissues of the NOSE or THROAT. Long-term topical corticosteroids can cause thinning and darkening of the SKIN.

Long-term systemic corticosteroid therapy, such as for immunosuppression or to treat severe autoimmune disorders, has numerous side effects that require close monitoring to maintain optimal health. Key among them are increased risks for type 2 DIABETES and OSTEOPOROSIS. Systemic corticosteroids alter the body's hormonal balance and interactions, affecting numerous endocrine functions such as regulatory mechanisms for INSULIN–GLUCOSE METABOLISM and calcium balance in the bones. Systemic corticosteroids also influence thyroid hormones, which may alter overall metabolism to result in side effects such as rapid weight gain (with a characteristic rounded face) and excessive tiredness. Some people experience mood swings, mood disorders, DEPRESSION, or GENERAL ANXIETY DISORDER (GAD) when taking long-term corticosteroid therapy, a consequence of the influence corticosteroids exert on BRAIN neurotransmitters.

Because they suppress the immune response and LEUKOCYTE (white blood cell) production, systemic corticosteroids also increase the risk for infection. Chronic COLDS, URINARY TRACT INFECTION (UTI), CANDIDIASIS (yeast infection), and wounds that are slow to heal are common with long-term systemic corticosteroid therapy. Early treatment with ANTIBIOTIC MEDICATIONS or ANTIFUNGAL MEDICATIONS can help the body fight such infections. Systemic corticosteroids interact with numerous other medications and, because they cause sodium and fluid retention, may increase BLOOD PRESSURE or cause HYPERTENSION.

See also BONE; CUSHING'S SYNDROME; DRUG INTERACTION; 5-AMINOSALICYLATE (5ASA) MEDICATIONS; NEUROTRANSMITTER; NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS); OPPORTUNISTIC INFECTION; ORGAN TRANSPLANTATION; PSYCHOSIS; THYROID GLAND; WOUND CARE.

cytokines A large family of proteins that mediate and regulate the IMMUNE RESPONSE. Leukocytes (white BLOOD cells) produce cytokines. There are more than 100 cytokines, which may act independently or synergistically with other cytokines. Among the actions of cytokines are cell homing and direction (drawing leukocytes to the site of INFECTION or injury), INFLAMMATION response, and stimulation of the numerous molecules that participate in the immune response. Cytokines may act on the cells that produce them (autocrine activity), on cells in proximity to them (paracrine activity), or on cells throughout the body (endocrine activity).

MAJOR TYPES OF CYTOKINES

CHEMOKINES	COLONY-STIMULATING FACTORS (CSFS)
ERYTHROPOIETIN (EPO)	INTERFERONS
INTERLEUKINS	LYMPHOKINES
MONOKINES	TUMOR NECROSIS FACTORS (TNFS)

See also ANTIBODY; ANTIGEN; CELL-MEDIATED IMMUNITY; HISTAMINE; HORMONE; LEUKOCYTE; LEUKOTRIENES.

D

desensitization A therapeutic method in which gradual exposure to an ALLERGEN builds up the body's tolerance for the allergen, diminishing the IMMUNE RESPONSE to encountering it. IMMUNOGLOBULIN E (IgE) is primarily responsible for the symptoms associated with type I HYPERSENSITIVITY REACTION (allergic reaction), initiating the release of histamines, LEUKOTRIENES, and PROSTAGLANDINS. These substances induce INFLAMMATION (swelling), itching, sneezing, coughing, and other physiologic responses that represent the body's attempt to rid itself of the offending substance. Desensitization gradually activates an immunoglobulin G (IgG) ANTIBODY that binds, instead of IgE, with the allergen. Because IgG does not activate mast cells, the binding produces none of the symptoms that characterize a type I hypersensitivity reaction.

In desensitization the allergist injects the person with very small amounts of the allergen ("allergy shots") regularly over a period of three to five years. Relief is generally apparent in about a year. Approximately 80 percent of people who have seasonal allergies respond to desensitization, bringing their hypersensitivity reactions within tolerable parameters or eliminating them entirely. Desensitization, sometimes called allergy IMMUNOTHERAPY, is also highly effective for allergies to pet dander (especially cats), molds, and insect stings. Desensitization may be a therapeutic option for severe FOOD ALLERGIES that are difficult to manage by avoiding the food.

Desensitization injections carry the risk for instigating a severe hypersensitivity reaction including ANAPHYLAXIS, though this is rare. Some people experience temporary discomfort with the shots. Most people who undergo desensitization treatment have few side effects, however, and find the long-term benefit of reduced hypersensitivity reaction greatly improves their QUALITY OF LIFE.

See also ALLERGIC ASTHMA; ALLERGIC CONJUNCTIVITIS; ALLERGIC RHINITIS; ALLERGY; ALLERGY TESTING; ASTHMA; COUGH; HISTAMINE; LIVING WITH ALLERGIES; MAST CELL; SNEEZE.

disease-modifying antirheumatic drugs (DMARDs) Medications that alter the IMMUNE RESPONSE slow or stop the progression of certain degenerative, AUTOIMMUNE DISORDERS. The most common use of DMARDs is to treat RHEUMATOID ARTHRITIS. DMARDs provide relief from symptoms such as INFLAMMATION and PAIN, and in many people also reduce the JOINT deformities associated with rheumatoid arthritis and other degenerative conditions that result from the same disease process (such as ANKYLOSING SPONDYLITIS).

DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (DMARDS)

anti-TUMOR NECROSIS FACTORS (TNFS)	azathioprine
chloroquine	cyclophosphamide
cyclosporine	etanercept
gold salts	hydroxychloroquine
infliximab	leflunomide
methotrexate	penicillamine
sulfasalazine	

How These Medications Work

DMARDs work by altering or suppressing the immune response. Some of the DMARDs are immunosuppressive CHEMOTHERAPY drugs (such as methotrexate and cyclosporine), though researchers do not fully understand how they work to reduce autoimmune inflammation. Other DMARDs are antimalarial medications that suppress immune function by blocking the action of

enzymes involved in the inflammatory process. Anti-TNFs are MONOCLONAL ANTIBODIES (MABS) that block the release of TUMOR NECROSIS FACTORS (TNFs), CYTOKINES that influence inflammation during the immune response.

Therapeutic Applications

Because DMARDs can have significant and serious side effects, doctors prescribe them when other therapies are no longer effective. The most common use of DMARDs is to treat rheumatoid arthritis. Doctors also may prescribe DMARDs to treat another degenerative autoimmune arthritis, ankylosing spondylitis, and sometimes to treat other autoimmune conditions such as MYASTHENIA GRAVIS and SYSTEMIC LUPUS ERYTHEMATOSUS (SLE).

Risks and Side Effects

DMARDs can have significant and harmful side effects including DIARRHEA, RASH, ANEMIA, LEUKOPENIA, and increased risk for INFECTION, particularly OPPORTUNISTIC INFECTION, as a consequence of immunosuppression. Methotrexate can cause irreversible CIRRHOSIS and lung damage. A rare and potentially fatal adverse reaction to methotrexate is TOXIC EPIDERMAL NECROLYSIS (also called Stevens-Johnson syndrome). Chloroquine and hydroxychloroquine can cause vision disturbances and RETINOPATHY (permanent damage to the RETINA, resulting in VISION IMPAIRMENT).

DMARDs may also interfere with the actions of other medications. It is important to check with the doctor before using any additional medications, incuding over-the-counter products. Because of the potential risks these side effects have, doctors prescribe most non-MAb DMARDs for people whose conditions are not responding to other treatments.

See also CORTICOSTEROID MEDICATIONS; NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS).

F

5-aminosalicylate (5ASA) medications Drugs taken to treat INFLAMMATORY BOWEL DISEASE (IBD), an autoimmune disorder that causes mild to severe INFLAMMATION and irritation to the COLON (bowel). People who have IBD typically experience alternating periods of exacerbation and REMISSION; in severe IBD the symptoms are often debilitating. The aminosalicylates, or 5ASAs, appear to work by suppressing the local IMMUNE RESPONSE in the mucosal lining of the SMALL INTESTINE and COLON.

Though researchers do not fully understand what causes IBD, they do know there are high levels of LEUKOTRIENES and PROSTAGLANDINS in the BLOOD circulation when IBD flares up. Researchers believe the 5ASA medications block these biochemicals from release, thus inhibiting inflammation. These drugs may also block the actions of TUMOR NECROSIS FACTORS (TNFS), CYTOKINES that also participate in the inflammatory response.

5-AMINOSALICYLATE (5ASA) MEDICATIONS

balsalazide (Colazal)
mesalamine (Asacol, Canasa, Pentasa, Rowasa)
olsalazine (Dipentum)
sulfasalazine (Azulfidine)

The 5ASAs are most effective when administered via rectal suppository or ENEMA, or by absorption-delayed oral medications (drugs that are specially coated to dissolve in the SMALL INTESTINE rather than the STOMACH) as these ROUTES OF ADMINISTRATION deliver the drug directly to the involved tissues. Pharmacologically, the 5ASAs are similar to aspirin. The most common side effects include HEADACHE, NAUSEA, and RASH (which occur most frequently with sulfasalazine and not so much with the other 5ASAs). The 5ASAs are effective for treating symptoms during exacerbations as well as for extending remission (preventing symptoms from reemerging).

See also AUTOIMMUNE DISORDERS; CORTICOSTEROID MEDICATIONS; NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS).

food allergies Hypersensitivity reactions to consumed foods. Food allergies affect about nine million Americans, two thirds of them children under the age of six. Allergies to peanuts, milk, wheat, shellfish, strawberries, and eggs are among the most common. Some people are allergic to preservatives or other substances used to prepare foods. Children tend to outgrow many food allergies; however, many adults develop food allergies later in life.

Unpleasant responses—such as STOMACH irritation, FLATULENCE (intestinal gas), and episodes of DIARRHEA—to certain foods are common but are not necessarily food allergies. An ALLERGY results in the activation of antibodies that triggers a HYPERSENSITIVITY REACTION, an excessive IMMUNE RESPONSE in which the IMMUNE SYSTEM responds to a particular food as though it were a harmful substance. The COMPLEMENT CASCADE floods the BLOOD circulation with antibodies, mast cells release HISTAMINE and PROSTAGLANDINS, and various types of leukocytes mobilize to attack the ALLERGEN.

Though some symptoms may be the same—such as stomach upset and diarrhea—the difference between food intolerance and food allergy can literally be life threatening: ANAPHYLAXIS, the most severe kind of hypersensitivity reaction, is an ever-present danger with food allergies. Of particular concern are ingredients that may not be obvious, such as peanut oil or soy, and may be present in processed foods as cross-contaminants.

Symptoms and Diagnostic Path

A hypersensitivity reaction to a food produces symptoms that may include

- itching and swelling around the face, on the lips, and in the MOUTH
- nasal congestion
- wheezing or difficulty BREATHING
- sensation of a lump in the THROAT
- gastrointestinal PAIN (resulting from swelling in the intestinal mucosa)
- moderate to extensive diarrhea

More generalized symptoms such as SKIN rash, hives (URTICARIA), and ANGIOEDEMA are also possible. Symptoms may occur within minutes to 2 hours after eating the food. Anaphylaxis may develop with any hypersensitivity reaction, even when previous reactions have been mild.

ANAPHYLAXIS is a medical emergency that requires immediate treatment from a doctor. Tingling and swelling of the lips, tongue, and THROAT 20 to 60 minutes after eating a food for which there could be an allergy are possible indications of anaphylaxis.

When there is a clear connection between a specific food and a hypersensitivity response, identifying the allergen is fairly straightforward. When the connection is not clear, the diagnostic path can be arduous and may include

- blood tests to measure IMMUNOGLOBULIN E (IgE) levels
- ALLERGY TESTING with suspect substances
- elimination diet

The elimination diet involves removing suspected foods or foods that are common allergens from the diet, usually for two weeks, and then reintroducing them one at a time until symptoms recur. The last food reintroduced is the likely allergen. An elimination diet is appropriate only for people who have mild to moderate hypersensitivity reactions. The risk for anaphylaxis is too great to use the elimination diet approach in people who have had severe allergy symptoms such as wheezing, breathing difficulty, or urticaria (hives). No single diagnostic approach works for all food allergies; diagnosis becomes a process of drawing conclusions based on symptoms.

COMMON FOOD ALLERGIES

cow's milk	eggs
peanuts	shellfish (lobster, shrimp, crab)
soy	strawberries
tree nuts (almonds, cashews, walnuts, pecans)	wheat (including flour)

Treatment Options and Outlook

A moderate hypersensitivity reaction may require treatment with ANTIHISTAMINE MEDICATIONS; a serious reaction may require a course of oral CORTICOSTEROID MEDICATIONS to halt the immune response and relieve the discomfort of the symptoms. Many hypersensitivity reactions to foods produce mild symptoms that go away without treatment. A doctor should evaluate symptoms that do not improve within a few days.

The most effective long-term treatment is to avoid the allergen. This is not always as easy as it sounds because often variations of the allergen are ingredients in prepared or baked foods. Peanuts, eggs, milk, soy, and wheat are common in many foods. Cross-contamination is also a concern, particularly among processed foods manufactured in facilities that use various ingredients in different products. An ice cream manufacturer may make a flavor that has nuts, for example, and then use the same equipment to make a flavor that does not have nuts. Even residue not visible to the eye can be sufficient to cause a hypersensitivity reaction in someone who is highly allergic. Labels on packaged foods include information about whether the product comes from a facility in which cross-contamination is possible. People who have food allergies must ask about obvious as well as hidden ingredients when eating away from home.

DESENSITIZATION (allergy shots) is a therapeutic option for people who have allergies to foods that are especially common or who have severe hypersensitivity reactions. Though it takes up to two years for desensitization to reach its maximum effectiveness, most people notice a reduced hypersensitivity reaction within six months.

Risk Factors and Preventive Measures

People who have other allergies or who have family members who have food allergies are more likely to develop food allergies. There are no measures to prevent allergies, food or otherwise. Identifying and avoiding foods that cause hypersensitivity reactions are the most effective methods for preventing those reactions and their unpleasant symptoms. Many people who have food allergies are able to manage them by carefully reading product labels and asking about ingredients when eating away from home.

See also ANTIBODY; ANTIGEN; BREATH SOUNDS; CARBOHYDRATE INTOLERANCE; CELIAC DISEASE; FOODBORNE ILLNESSES; LACTOSE INTOLERANCE; LEUKOCYTE; LIVING WITH ALLERGIES; MAST CELL.

G

gammaglobulin A solution of immunoglobulins collected from the PLASMA of donated BLOOD or from donated plasma. The highest concentration is of IMMUNOGLOBULIN E (IgE). Health-care providers administer gammaglobulin by intramuscular or intravenous injection to provide rapid immune protection for exposure to infectious diseases such as HEPATITIS. Though the protection is temporary, it helps prevent INFECTION until the person's IMMUNE SYSTEM can produce the necessary antibodies. Gammaglobulin is the treatment of choice when there is widespread public exposure to infectious diseases, such as may occur in schools and day-care centers.

See also ANTIBODY; ANTIGEN; IMMUNITY.

graft vs. host disease A life-threatening condition in which the immune cells (leukocytes and lymphocytes) contained in allogeneic transplanted BONE MARROW (the graft, from a donor source) produce antibodies that attack other organs in the organ transplant recipient's body (the host). BONE MARROW TRANSPLANTATION (or BLOOD STEM CELLtransplantation) is the primary treatment for cancers of the BLOOD such as LEUKEMIA, lymphoma, and MULTIPLE MYELOMA. Doctors may also use bone marrow transplantation to treat some types of cancer that do not respond to other therapies, severe aplastic ANEMIA, and severe SICKLE CELL DISEASE.

Graft vs. host disease is not a threat with autologous (self) bone marrow transplantation, which re-infuses blood stem cells previously withdrawn from the person. The condition occasionally develops after solid ORGAN TRANSPLANTATION and in IMMUNOCOMPROMISED people who receive BLOOD TRANSFUSIONS.

The immune cells of the transplanted bone marrow generate antibodies that commonly attack the recipient's LIVER, gastrointestinal tract (especially the STOMACH and SMALL INTESTINE), and SKIN. Damage can be rapid and severe. When the condition involves multiple organs, as is common, catastrophic multiple system failure is very possible. Graft vs. host disease accounts for more deaths after 100 days past the bone marrow transplantation than any other cause, including the cancer under treatment.

Symptoms and Diagnostic Path

Acute graft vs. host disease occurs within 100 days after the transplantation. About 30 percent of bone marrow transplant recipients experience acute symptoms, which may include

- skin RASH
- DIARRHEA
- INFECTION

Chronic graft vs. host disease develops or continues beyond 100 days from transplantation, though typically chronic disease tends to first manifest between 3 and 12 months after the transplant. The perpetual attacks that are the hallmark of chronic graft vs. host disease result in fibrotic (SCAR-related) changes to the skin, liver, and LUNGS. About 70 percent of people who receive bone marrow transplants experience some degree of chronic symptoms, which typically include

- dry, itchy skin
- discolored or taut skin
- HAIR loss or graying
- weight loss
- shortness of breath with exertion (DYSPNEA)

- chronic fatigue
- dry eyes and MOUTH

The diagnostic path includes blood tests to measure blood cell types and counts, ANTIBODY levels, and liver enzymes. In particular, CD-4+ and CD-8+ T-lymphocytes are abundant. Tissue biopsies also show evidence of damage due to the immune attack. Doctors classify graft vs. host disease into four stages, according to the severity of symptoms; stage 1 is the mildest and stage 4, the most severe.

Treatment Options and Outlook

At present the most successful treatment is IMMUNOSUPPRESSIVE THERAPY. Ideally, prophylactic immunosuppression prevents graft vs. host disease. When symptoms occur, immunosuppression can minimize the consequences and limit damage. Immunosuppression itself carries significant risk, however. The risk for infection, especially an OPPORTUNISTIC INFECTION the IMMUNE SYSTEM could normally keep at bay, is very high. CORTICOSTEROID MEDICATIONS, the cornerstone of immunosuppressive therapy, cause serious side effects with long-term, systemic use. As well, some immunosuppressive agents are chemotoxic (they work by killing cells) and have harmful side effects. The balance between sufficient immune suppression and adequate immune function is delicate.

Other treatment options include MONOCLONAL ANTIBODIES (MABS), which bind with the ANTIGEN receptors on the cell membrane surfaces of the cells in the organ. However, the body may develop antibodies against the MAbs. Though the first treatment is successful, subsequent efforts with the same MAbs will initiate an immune attack against the MAbs. A number of clinical trials are exploring investigational treatments for graft vs. host disease. A key challenge in treatment is that, although doctors fully understand what happens during graft vs. host disease, the mechanisms by which events occur remain unknown.

Risk Factors and Preventive Measures

Anyone who has bone marrow transplantation is at risk for graft vs. host disease. Optimal matching of HUMAN LEUKOCYTE ANTIGENS (HLAS) before trans-

ACUTE GRAFT VS. HOST DISEASE STAGING

Stage	Degree of Severity	Symptoms
1	mild	SKIN RASH affecting less than 25 percent of the skin surface, often starting on the hands and feet no other symptoms
2	moderate	skin rash affecting more than 25 percent of the skin surface mild gastrointestinal discomfort and DIARRHEA mild JAUNDICE
3	severe	extensive SUNBURN-like rash over most of the body STOMACH discomfort, abdominal cramping, diarrhea frequent or chronic INFECTION nutritional deficiencies moderate jaundice and LIVER dysfunction
4	life threatening	skin blisters and peeling skin over most of the body gastrointestinal PAIN bloody diarrhea severe jaundice and significant liver dysfunction or LIVER FAILURE serious INFECTION or OPPORTUNISTIC INFECTION malabsorption of NUTRIENTS

plantation provides the most successful circumstance for preventing graft vs. host disease. When precise HLA matching is not possible, screening for and selectively removing some T-cell lymphocytes (CD-4+ and CD-8+) from the donor organ that carry antibodies likely to attack the recipient can reduce the risk for graft vs. host disease. The risk for graft vs. host disease is also higher for people who receive blood stem cells extracted from donated blood (rather than from bone marrow donation), except cord stem cells extracted from umbilical blood.

See also CLUSTERS OF DIFFERENTIATION; LEUKOCYTE; LIVING WITH IMMUNE DISORDERS; LYMPHOCYTE; MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT); STEM CELL; STEM CELL THERAPY; SURGERY BENEFIT AND RISK ASSESSMENT.

granuloma An accumulation of granulocytes (also called polymorphonuclear leukocytes [PMNs]) and other cells that contain and enclose an area of INFLAMMATION at the site of cell injury, usually due to INFECTION. The effect is to "wall off" the area so the infection cannot spread. The resulting construction is fibrous (SCAR-like). Over time the PATHOGEN causing the infection within the granuloma dies but the granuloma remains. Granulomas may form anywhere in the body. CYTOKINES are instrumental in facilitating the process of granuloma formation, directing the actions of the involved immune cells.

Granulomas in the LUNGS commonly result from HISTOPLASMOSIS and other fungal infections. Granuloma inguinale is a sexually transmitted disease (STD). Granulomas are also characteristic of TUBERCULOSIS, Hansen's disease (leprosy), and SARCOIDOSIS. Any underlying infectious disease requires appropriate treatment. The doctor may surgically remove granulomas that cause discomfort or are unsightly. The granuloma itself usually causes no problems and does not require treatment.

See also FUNGUS; GRANULOCYTE; LEUKOCYTE; PHAGOCYTE; PHAGOCYTOSIS; SEXUALLY TRANSMITTED DISEASES (STDS).

gut-associated lymphoid tissue (GALT) Loosely organized, nonencapsulated clusters of LYMPH tissue beneath the epithelium (tissue that forms the mucous lining) of the gastrointestinal tract from the ESOPHAGUS to the COLON. T-cell lymphocytes, B-cell lymphocytes, and macrophages primarily inhabit GALT. The role of GALT is to block NORMAL FLORA BACTERIA (bacteria that are normally present in the gastrointestinal tract to aid digestion) from penetrating into other tissues or the BLOOD circulation. GALT also helps prevent gastrointestinal viruses from causing INFECTION. The presence of GALT in the lining of the STOMACH increases with aging. GALT also includes the small, nodelike lymphoid structures called PEYER'S PATCHES that pepper the SMALL INTESTINE. Peyer's patches intensify the presence of the IMMUNE SYSTEM and are the sites of much ANTIBODY activity from B-lymphocytes.

See also LYMPH NODE; LYMPHOCYTE; MACROPHAGE; MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT); NOSE-ASSOCIATED LYMPHOID TISSUE (NALT); PATHOGEN; PHAGOCYTE; PHAGOCYTOSIS; SKIN-ASSOCIATED LYMPHOID TISSUE (SALT); VIRUS.

H

hay fever See ALLERGIC RHINITIS.

healing The processes and mechanisms by which the body repairs itself. Healing represents complex and cascading interactions among various of the body's systems and mechanisms. Among the first to respond are the COAGULATION cascade, to stop bleeding, and the IMMUNE RESPONSE, which mobilizes T-cell lymphocytes, macrophages, antibodies, the COMPLEMENT CASCADE, and the release of CYTOKINES and PROSTAGLANDINS. Fibroblasts (cells that build collagen) converge at the site about 48 hours after the injury occurs to begin construction of SCAR tissue. After about six weeks the healing process turns its focus to remodeling the collagen tissue, restoring the tissues at the site of the injury to relatively normal structure and appearance. This final phase of healing lasts six months to two years, depending on the extent of the injury.

Disease processes influence healing as well. Chronic conditions such as DIABETES and PERIPHERAL VASCULAR DISEASE (PVD), themselves likely the result of inflammatory dysfunction of some sort, damage the fine networks of nerves and BLOOD vessels that intertwine through the tissues, limiting the ability of these structures to carry signals (nerves) and transport molecules and cells vital to immune function (blood vessels). Serious injury—whether from disease process, trauma, or major surgery—affects endocrine and hormonal activity throughout the body, which influence the rate and processes of healing. Serious injury temporarily stuns the THYROID GLAND, for example, resulting in reduced production of thyroid hormones and consequential slowing of METABOLISM (EUTHYROID SICK SYNDROME).

Although researchers can map the physiologic steps of healing, much of healing remains a mystery. Researchers do not fully understand what starts, regulates, and ends the healing process. Many integrations across neurologic, endocrine, and immune functions are factors in healing. Some researchers are exploring connections between emotions and the numerous biochemical substances that are key to the healing process. Researchers know, for example, that emotional stress influences the release of numerous hormones in the body and the release of these hormones—such as the hormone CORTISOL, a powerful immunosuppressant—directly affects the functions of the IMMUNE SYSTEM. Research has shown that pain is a stressor and affects the rate of healing. Studies continue to explore the relationship between the mind and healing.

See also AYURVEDA; HORMONE; INTEGRATIVE MEDICINE; MIND–BODY INTERACTIONS; PATHOGEN; REIKI; STRESS RESPONSE HORMONAL CASCADE; TRADITIONAL CHINESE MEDICINE (TCM); WOUND CARE.

histamine A chemical that acts as an IMMUNE RESPONSE mediator. Large, granulated leukocytes called mast cells, which reside in the mucous membrane lining of the respiratory and gastrointestinal tracts, store histamine in their granules and release it during the immune response. Mast cells are most abundant in the nasal passages (including the SINUSES), the TRACHEA, and the bronchi. Histamine receptors on the surfaces of cell membranes determine how histamine affects the cell. ANTIHISTAMINE MEDICATIONS, the cornerstone of treatment for type I HYPERSENSITIVITY REACTION (allergic reaction), work by blocking histamine receptors.

Though there is only one form of histamine, its release can activate any of three types of histamine receptors: H1, H2, and H3. CYTOKINES,

PROSTAGLANDINS, and other biochemical messengers determine histamine release and what histamine binding will occur. Each histamine receptor regulates a different response:

- H1 receptors are on cell membrane surfaces of arteriole and capillary cells. H1 binding causes the arterioles to dilate (open) and the capillaries to increase the permeability of their walls. The effect of these actions is to allow additional fluid to seep from these blood vessels into the interstitial spaces (spaces between cells). The fluid floods the cells with INFECTION-fighting molecules, notably antibodies and cytokines. IMMUNOGLOBULIN E (IgE) binds with antigens and allergens, triggering H1 release. H1 is primarily responsible for type I hypersensitivity reactions such as ALLERGIC RHINITIS and ALLERGIC ASTHMA. Common antihistamine medications that block H1 receptor binding include diphenhydramine, chlorpheniramine, and hydroxyzine.
- H2 receptors are in parietal cells of the STOMACH. H2 binding acts to increase the flow of gastric acid in the stomach. Excessive secretion of histamine binding with H2 receptors is primarily responsible for GASTROESOPHAGEAL REFLUX DISORDER (GERD). Medications to limit histamine secretion and H2 receptor binding include H2 ANTAGONIST (BLOCKER) MEDICATIONS such as cimetidine and ranitidine.
- H3 receptors are neuroreceptors in the CENTRAL NERVOUS SYSTEM with high concentration in the areas of the HYPOTHALAMUS that regulate alertness. H3 binding decreases NEURON (NERVE cell) secretion of histamine, serotonin, acetylcholine, EPINEPHRINE, and NOREPINEPHRINE. The effect is to reduce alertness, which takes place as a natural aspect of the circadian cycle (body's rhythm of sleep and wakefulness). These neurotransmitters also affect the NAUSEA center. The antihistamine medications doxylamine and hydroxyzine are highly effective H3 receptor blockers.

Doctors typically consider only H1 receptor binding in the context of the immune response and focus primarily on whether its actions to initiate INFLAMMATION are helpful or counterproductive.

See also ALLERGEN; ANTIBODY; ANTIGEN; LEUKOCYTE; LEUKOTRIENES; MAST CELL; NEURORECEPTOR; NEUROTRANSMITTER; PROTON PUMP INHIBITOR (PPI) MEDICATIONS.

human leukocyte antigens (HLAs) Unique proteins (antigens) present on every nucleated cell (cell that has a nucleus) in the body. Also called histocompatibility locus antigens, HLAs allow the IMMUNE SYSTEM to identify cells as self (belonging to the body). Genes on CHROMOSOME 6, in a region called the MAJOR HISTOCOMPATIBILITY COMPLEX (MHC), regulate HLAs. Each person has unique HLAs. The nomenclature (naming convention) for HLAs identifies the ALLELE and GENE locus (position on the chromosome), designating the former with a letter and the latter with a number.

HLAs have various immune roles, including identification of self and nonself cells. This function makes HLAs of crucial importance in ORGAN TRANSPLANTATION. Incompatibility in HLAs can result in GRAFT VS. HOST DISEASE and rejection of the transplanted organ. IMMUNOSUPPRESSIVE THERAPY to subdue the IMMUNE RESPONSE in people who have organ transplants in part targets HLAs. Some research suggests that HLAs also may play crucial roles in the development of AUTOIMMUNE DISORDERS such as SYSTEMIC LUPUS ERYTHEMATOSUS (SLE), MULTIPLE SCLEROSIS, and SJÖGREN'S SYNDROME.

Though there are nearly endless configurations of HLAs, there are three broad groups of HLAs: HLA-A, HLA-B, and HLA-DR. Each set of three is called a haplotype. Every person has two specific HLAs from each of the three groups, for a total of two haplotypes (six HLAs). Each parent passes one haplotype to each child. Tissue matching for organ transplantation compares the donor's six HLAs with the recipient's six HLAs. The more that match, the more likely the organ transplant will be successful. The fewer that match, the greater the risk that the recipient's immune system will attack the donor organ.

The other key factor in HLA matching is immune reactivity (ANTIBODY reaction). It is possible to develop antibodies to HLAs that, even with a match, make it almost certain that the recipient will reject the organ. The most common cause for HLA antibodies is exposure to nonself HLA as a result of BLOOD TRANSFUSION. HLA matching is not a

component of blood typing. It is possible to have immune reactivity to multiple HLA proteins, which increases the difficulty of locating a good match for organ transplantation. Typically transplant centers like to see a match on four or more of the HLAs. A match of three or fewer strongly suggests the recipient will reject the transplanted organ.

See also ANTIBODY-MEDIATED IMMUNITY; ANTIGEN; GENOTYPE; INHERITANCE PATTERN; PHENOTYPE.

humoral immunity See ANTIBODY-MEDIATED IMMUNITY.

hypersensitivity reaction A symptomatic interaction between antibodies and allergens that causes an exaggerated and harmful response in the body, commonly called an allergic reaction. Hypersensitivity reactions range from mild to life threatening in severity and symptoms.

ANAPHYLAXIS, the most severe hypersensitivity reaction, is a life-threatening emergency that requires immediate medical attention.

There are four types of hypersensitivity reaction, classified according to the way in which the ALLERGEN or ANTIGEN activates the reaction. The classic allergic reaction is the type I hypersensitivity reaction, with exposure to an external substance (the allergen) initiating the IMMUNE RESPONSE. Types II, III, and IV hypersensitivity reactions are endogenous (within the body) responsible for IMMUNE DISORDERS (other than due to IMMUNODEFICIENCY) and AUTOIMMUNE DISORDERS.

Type I Hypersensitivity Reaction: IgE Antibody Reaction

IMMUNOGLOBULIN E (IgE), the foundation lipoprotein for ANTIBODY formation, mediates type I hypersensitivity reactions. With exposure to an external allergen, the immune response floods the BLOOD circulation with antibodies. Mast cells, basophils, and eosinophils (white blood cells that have specialized immune functions) participate in type I hypersensitivity reactions. Mast cells release HISTAMINE, PROSTAGLANDINS, and other biochemicals that set in motion interactions among various proteins and cells that guide further immune activity.

Symptoms generally occur within 15 to 30 minutes of exposure, though sometimes can emerge 10 to 12 hours after exposure. Anaphylaxis (also called anaphylactic shock) is the most severe type I hypersensitivity and is life threatening. ALLERGIC RHINITIS, ALLERGIC CONJUNCTIVITIS, ALLERGIC ASTHMA, ATOPY, and FOOD ALLERGIES are type I hypersensitivity reactions. Type I hypersensitivity reactions tend to run in families, causing researchers to suspect genetic underpinnings for the allergies.

A type I hypersensitivity reaction occurs in two stages: the induction stage, the first exposure during which the IMMUNE SYSTEM produces antibodies for the particular antigen or allergen, and the elicitation stage, during which the immune response activates the antibodies to attack the antigen or allergen. There are no symptoms during the induction stage. Each subsequent exposure to the antigen or allergen triggers the elicitation stage, resulting in symptoms. The elicitation stage lasts as long as there is allergen–antibody interaction, though symptoms may continue for some time (hours to days) afterward.

Regardless of what form symptoms take (SKIN RASH, tingling around the MOUTH, DIARRHEA), a type I hypersensitivity reaction is a systemic response—it affects and involves the body as a whole. Sensitization to an allergen is long term or lifelong because the antibody-bearing PLASMA cells (B-cell lymphocytes that specialize to produce antibodies) circulate indefinitely in the blood.

Type II Hypersensitivity Reaction: Cytotoxic Reaction

Immunoglobulin G (IgG) and immunoglobulin M (IgM) mediate cytotoxic reactions, also called antibody-mediated hypersensitivity reactions. Type II reactions occur as a result of interactions between antibodies and antigens on cell membrane surfaces. The immune response activates the COMPLEMENT CASCADE, which results in the release of biochemicals that kill the antigen-bearing cells. T-cell lymphocytes and natural killer (NK) cells also participate. Symptoms of a type II hypersensitivity reaction typically emerge within a few minutes to several hours after antibody–antigen binding.

Hemolytic ANEMIA, BLOOD TRANSFUSION reactions, Rhesus (Rh) blood reactions (erythroblastosis fetalis), PEMPHIGUS, GOODPASTURE'S SYNDROME, and many DRUG allergies (notably penicillin) are type II hypersensitivity reactions.

Type III Hypersensitivity Reaction: Immune Complex (IC) Reaction

IgG and IgM also mediate type III hypersensitivity reactions, though through different mechanisms from those that occur in type II hypersensitivity reactions. Type III hypersensitivity reactions occur when unattached antigens enter the blood circulation and activate an immune response that results in the formation of an immune complex, a conglomeration of immune proteins (immunoglobulins), platelets, neutrophils, and immune-related substances that surround the antigens. Eventually these clumps fall out of the blood circulation and settle into tissues. Type III antibodies are autoantibodies—that is, antibodies that target the body's own antigens.

Researchers do not know what precipitates the immune response in most type III reactions, though viruses such as HEPATIS A, serum sickness, and drug reactions are sometimes accountable. Symptoms develop 3 to 10 hours after the immune complex forms. ASPERGILLOSIS, SYSTEMIC LUPUS ERYTHEMATOSUS (SLE), GLOMERULONEPHRITIS, polyarteritis and other forms of VASCULITIS, and RHEUMATOID ARTHRITIS are type III hypersensitivity reactions.

Type IV Hypersensitivity Reaction: Delayed Reaction

T-cell lymphocytes (primarily helper T-cells) mediate type IV hypersensitivity reactions, also called delayed-type hypersensitivity (DTH) or cell-mediated hypersensitivity reactions. Type IV reactions take days to weeks to manifest. The rash of poison ivy, poison oak, and poison sumac represents a type IV hypersensitivity reaction. GRANULOMA is also a typical type IV hypersensitivity reaction, often to BACTERIA or fungi the body is unable to completely eliminate. Common therapeutic applications of a type IV hypersensitivity reaction include the tuberculin skin test to detect the presence of *Mycobacterium tuberculosis* and skin patch ALLERGY TESTING.

Symptoms and Diagnostic Path

Symptoms vary with the type and severity of the hypersensitivity reaction. Itching and skin rash or URTICARIA (hives) are common with type I hypersensitivity reactions. Symptoms may involve the airways (allergic asthma) or gastrointestinal tract (food allergies). Contact reactions typically involve the surface of the skin though may also produce widespread systemic symptoms. The diagnostic path may include blood tests to assess the types and levels of blood cells present in the circulation as well as to detect the types and quantities of immunoglobulins. Allergy testing can help isolate the specific allergens for type I hypersensitivity reactions. The doctor may conduct further diag-

HYPERSENSITIVITY REACTION TYPES AND SYMPTOMS

Type of Reaction	Symptoms	Typical Onset from Exposure
type I (IgE antibodies)	URTICARIA (hives), SKIN RASH, wheezing itching	15 to 30 minutes
type II (cytotoxic)	redness and swelling due to cell or tissue death	minutes to several hours
type III (immune complex)	redness and swelling (erythema and edema) pain	3 to 10 hours
type IV (cell mediated)	redness and hardness (erythema and induration) PAIN	48 to 72 hours (nongranuloma) 3 to 4 weeks (granuloma)

nostic testing to rule out other possible causes of the symptoms.

Treatment Options and Outlook

Antihistamine medications are the most effective intervention early in the onset of a type I hypersensitivity reaction, the classic allergic reaction. These medications block histamine receptors on cell membrane surfaces, effectively breaking the chain reaction effect of the immune response. The longer the hypersensitivity reaction has been under way, the less effective antihistamine medications are because the reaction moves beyond histamine release and binding. Treatment for anaphylactic symptoms is injection with EPINEPHRINE, a potent NEUROTRANSMITTER and HORMONE that effectively halts the immune response. Doctors reserve epinephrine for life-threatening hypersensitivity reactions because the drug has numerous and significant effects on cardiovascular and pulmonary function.

CORTICOSTEROID MEDICATIONS are effective for severe type I reactions and type II, III, and IV reactions. Other IMMUNOSUPPRESSIVE MEDICATIONS such as methotrexate and cyclosporine act through different mechanisms to interrupt the immune response. DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (DMARDS) use various mechanisms to achieve similar results. MONOCLONAL ANTIBODIES (MABS) are showing great promise for treating hypersensitivity reactions in some people. The appropriate treatment selections depend on the type and severity of the hypersensitivity reaction and any other health conditions the person may also have.

TREATMENT OPTIONS FOR HYPERSENSITIVITY REACTION

Treatments	Effects	Effective for Type of Reaction
ANTIHISTAMINE MEDICATIONS	block HISTAMINE binding	type I
CORTICOSTEROID MEDICATIONS	suppress COMPLEMENT CASCADE, ANTIBODY activation, and eosinophil production suppress mast cell release of histamine, LEUKOTRIENES, and PROSTAGLANDINS	type II, type III, type IV type I when severe or nonresponsive to other treatment
DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (DMARDS)	suppress various immune response pathways	type III
EPINEPHRINE injection	stop the immune response	type I when severe or anaphylactic
immunosuppressive agents other than corticosteroids	suppress various immune response pathways	type III and type IV
leukotriene receptor antagonist medications	block leukotriene binding	type I when ASTHMA present
MAST CELL stabilizers	prevent degranulation within mast cells to block the release of histamine, leukotrienes, and prostaglandins	type I when asthma present
MONOCLONAL ANTIBODIES (MABS)	block antibody–ANTIGEN binding	type I when asthma present type III and type IV
NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)	block the actions of prostaglandins	type III

Risk Factors and Preventive Measures

The sole risk for hypersensitivity reaction (types I, II, and III) is exposure to an allergen; the most effective prevention is avoiding such exposure. This approach is often easier said than done, especially when the allergen is an ubiquitous substance such as pollen or mold. Doctors often recommend taking antihistamine medications on a regular schedule during times when pollen counts are high to reduce hypersensitivity reactions among people who have seasonal allergies. Desensitization effectively reduces or prevents hypersensitivity reactions to specific allergens for many people, providing permanent relief.

See also ALLERGIC DERMATITIS; ALLERGY; B-CELL LYMPHOCYTE; GRANULOCYTE; LEUKOCYTE; LIVING WITH ALLERGIES; LYMPHOCYTE; MAST CELL; NATURAL KILLER (NK) CELL; T-CELL LYMPHOCYTE.

I

immune disorders Chronic conditions of the IMMUNE SYSTEM that affect the IMMUNE RESPONSE and the body's ability to protect and defend itself against INFECTION. Immune disorders generally result from a deficiency or absence of some component or structure of immune function. Such a deficiency may be primary, which is congenital (present at birth), genetic (inherited), or acquired (develops during life). People who have had their spleen surgically removed (SPLENECTOMY) also have reduced immune response, which results in increased susceptibility to infection.

IMMUNE DISORDERS

AUTOIMMUNE DISORDERS	COMMON VARIABLE IMMUNE DEFICIENCY (CVID)
HIV/AIDS	IMMUNOGLOBULIN A (IgA) deficiency
HYPERSENSITIVITY REACTION	IgM deficiency
IgA NEPHROPATHY	SEVERE COMBINED IMMUNODEFICIENCY (SCID)
IgE deficiency	Wegener's granulomatosis
PARTIAL COMBINED IMMUNODEFICIENCY (PCID)	
TOXIC EPIDERMAL NECROLYSIS	

Frequent or chronic infection is the primary symptom of an immune disorder other than HYPERSENSITIVITY REACTION (allergy). BLOOD tests for immunoglobulins and antibodies generally can diagnose immune disorders. Hypersensitivity reactions generate symptoms according to the type of reaction and may include symptoms of ALLERGIC RHINITIS, ALLERGIC CONJUNCTIVITIS, ALLERGIC DERMATITIS, or ALLERGIC ASTHMA. ALLERGY TESTING is the preferred diagnostic approach for identifying the allergens responsible for hypersensitivity reaction, though often a person knows the cause of an allergy.

Immune disorders are generally chronic, which means treatment can improve symptoms but not cure or end the condition. Common medication therapies for immune disorders include ANTIHISTAMINE MEDICATIONS, NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS), CORTICOSTEROID MEDICATIONS, leukotriene receptor antagonists, MAST CELL stabilizers, and DISEASE-MODIFYING RHEUMATOID DRUGS (DMARDS). The particular medication regimen depends on the immune disorder and the individual's symptoms.

See also ANTIBODY; ATOPY; GENETIC DISORDERS; IMMUNITY; IMMUNOCOMPROMISED; IMMUNODEFICIENCY; LEUKOTRIENES; LIVING WITH IMMUNE DISORDERS.

immune response The multiple mechanisms and processes through which the body identifies and reacts to antigens. The immune response is the body's primary means of protecting itself from INFECTION. There are three independent yet complementary immune response pathways: ANTIBODY-MEDIATED IMMUNITY (also called humoral immunity), CELL-MEDIATED IMMUNITY, and the COMPLEMENT CASCADE. As well, the immune response stimulates activity from the NERVOUS SYSTEM and the endocrine system.

The immune response relies largely on ANTIBODY–ANTIGEN binding. Antigens are molecules that identify cells to the IMMUNE SYSTEM. Antibodies are molecules the immune system produces to bind with nonself antigens—antigens on cells that do not belong to the body. With antibody–antigen binding, the antibody releases proteins called opsonins that mark the antigen-bearing cell for destruction by killer T-cells and natural killer (NK) cells. Monocytes (in the BLOOD circulation) and macrophages (in the tissues) consume the cellular debris remaining after the marked cell's destruction. Antibody–antigen binding also activates the complement cascade, a biochemical response that

produces proteins that attach to and damage the cell membrane of cells that the immune response identifies as nonself.

A key feature of the immune response is INFLAMMATION, the process by which the body increases the ability of PLASMA, the liquid component of blood, to seep into the tissues (interstitial spaces). HISTAMINE and PROSTAGLANDINS are the primary agents of the inflammatory response. Inflammation floods the tissues with immune molecules to extend the immune response beyond the blood and the LYMPH. Inflammation also serves to contain the infection, keeping it from spreading beyond its point of origin to other areas of the body.

For further discussion of the immune response within the context of the structures and functions of the immune system, please see the overview section "The Immune System and Allergies."

See also ALLERGEN; ECHINACEA; GOLDENSEAL; HUMAN LEUKOCYTE ANTIGENS (HLAS); HYPERSENSITIVITY REACTION; MACROPHAGE; MAJOR HISTOCOMPATIBILITY COMPLEX (MHC); MAST CELL; MONOCYTE; NATURAL KILLER (NK) CELLS; PHAGOCYTOSIS.

immune system The structures, substances, and processes that protect the body from INFECTION. These include organs, tissues, cells, and molecules. The immune system functions in close collaboration with the NERVOUS SYSTEM and the endocrine system.

The main organs and tissues of the immune system include

- BONE MARROW
- THYMUS
- SPLEEN
- lymph nodes
- BLOOD
- LYMPH
- adenoids and tonsils
- APPENDIX
- MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT)
- SKIN
- tears
- saliva

The primary cells of the immune system include

- B-cell lymphocytes (PLASMA cells, memory B-cells)
- T-cell lymphocytes (helper T-cells, cytotoxic T-cells, memory T-cells, suppressor T-cells)
- granulocytes (neutrophils, eosinophils, and basophils)
- macrophages and dendritic cells
- mast cells
- monocytes
- M cells
- natural killer (NK) cells

Key molecules of the immune system include

- HUMAN LEUKOCYTE ANTIGENS (HLAS)
- complement factors
- CLUSTERS OF DIFFERENTIATION
- IMMUNOGLOBIN
- antigens
- antibodies
- PROSTAGLANDINS
- HISTAMINE
- LEUKOTRIENES
- CYTOKINES (CHEMOKINES, INTERLEUKINS, MONOKINES, INTERFERONS, LYMPHOKINES, COLONY-STIMULATING FACTORS [CSFS], and TUMOR NECROSIS FACTORS [TNFS])

For further discussion of the structures and functions of the immune system, please see the overview section "The Immune System and Allergies."

See also ANTIBODY; ANTIGEN; ANTIBODY-MEDIATED IMMUNITY; B-CELL LYMPHOCYTE; CELL-MEDIATED IMMUNITY; COMPLEMENT CASCADE; GRANULOCYTE; IMMUNE RESPONSE; LYMPH NODE; LYMPHOCYTE; MACROPHAGE; MAJOR HISTOCOMPATIBILITY COMPLEX (MHC); MONOCYTE; NATURAL KILLER (NK) CELL; PSYCHONEUROIMMUNOLOGY; T-CELL LYMPHOCYTE.

immunity An established base of protection against INFECTION. Immunity may be innate, pas-

sive, or acquired. INNATE IMMUNITY, also called natural immunity, is present at birth and provides effective protection against a broad base of common pathogens. Innate immunity is limited in scope. PASSIVE IMMUNITY is ANTIBODY-specific but present without activation of the IMMUNE RESPONSE. A newborn has passive immunity based on the antibodies present in his or her mother's BLOOD. BLOOD TRANSFUSION, PLASMA transfusion, and administration of GAMMAGLOBULIN also convey passive immunity to the recipient. Passive immunity is short term. The body develops acquired immunity through exposure to antigens via infection or vaccination. Acquired immunity is ANTIGEN-specific and long term, often lifelong.

For further discussion of immunity within the context of the structures and functions of the IMMUNE SYSTEM, please see the overview section "The Immune System and Allergies."

See also ANTIBODY-MEDIATED IMMUNITY; CELL-MEDIATED IMMUNITY; PATHOGEN; VACCINE.

immunoablation The therapeutic destruction of the body's IMMUNE RESPONSE, typically to prepare for BONE MARROW TRANSPLANTATION or STEM CELL transplantation. Immunoablation is usually a step in the treatment process for certain cancers and AUTOIMMUNE DISORDERS, such as severe MULTIPLE SCLEROSIS. High-DOSE CHEMOTHERAPY and RADIATION THERAPY are the most common methods of immunoablation. The goal is to remove all T-cell lymphocytes from the BLOOD, which destroys the body's CELL-MEDIATED IMMUNITY. Until the person's IMMUNE SYSTEM restores immune functions, the person is extremely vulnerable to any INFECTION. A person who has undergone immunoablation stays in a hospital in strict isolation until immune function returns after bone marrow or stem cell transplantation.

See also CANCER TREATMENT OPTIONS AND DECISIONS; LEUKEMIA; MULTIPLE MYELOMA; T-CELL LYMPHOCYTE.

immunocompromised Any circumstance in which the IMMUNE SYSTEM lacks the capacity, as the consequence of an acquired health condition or a medication SIDE EFFECT, to protect the body from INFECTION. DIABETES is the most common reason people become immunocompromised. People who are taking IMMUNOSUPPRESSIVE THERAPY after ORGAN TRANSPLANTATION or to treat severe AUTOIMMUNE DISORDERS are also immunocompromised. People who are immunocompromised often struggle to fight off common infections such as COLDS and URINARY TRACT INFECTION (UTI) and are vulnerable to OPPORTUNISTIC INFECTION (an infection that a healthy immune system would easily rebuff).

See also ANTIBIOTIC PROPHYLAXIS; IMMUNE DISORDERS; LIVING WITH IMMUNE DISORDERS.

immunodeficiency The absence of IMMUNE SYSTEM components essential for proper IMMUNE RESPONSE and protection from INFECTION. Immunodeficiency may be congenital (present at birth) or acquired (develop later in childhood or adulthood). As well, immunodeficiency is a consequence of therapies intended to compromise immune function, such as RADIATION THERAPY, CHEMOTHERAPY, and IMMUNOSUPPRESSIVE THERAPY.

Congenital immunodeficiency is genetic (the result of a GENE MUTATION) and may be inherited. Inherited immunodeficiencies can include IMMUNOGLOBULIN deficiencies, disorders of B-cell lymphocytes, disorders of T-cell lymphocytes, and complement disorders. A child born without a THYMUS or a SPLEEN will have multiple immunodeficiencies because these structures are crucial for LEUKOCYTE (white BLOOD cell) formation and maturation.

Acquired immunodeficiency generally occurs as a result of infections, AUTOIMMUNE DISORDERS, or severe trauma (such as BURNS) that challenges the immune system's capabilities. Conditions such as DIABETES and CYTOMEGALOVIRUS (CMV) infection commonly cause immunodeficiency. The HIV/AIDS infection is one of the most serious acquired immunodeficiencies, as it eventually destroys the immune system.

Immunodeficiency disorders are not currently preventable or curable; diligent treatment can usually keep disease progression and symptoms in check. Treatment for immunodeficiency disorders depends on the cause of the disorder and the symptoms it creates. Medications and IMMUNOTHERAPY (biologic response modification) allow many people who have immunodeficiency disorders live fairly normal lifestyles.

See also ANTIBODY-MEDIATED IMMUNITY; B-CELL LYMPHOCYTE; CELL-MEDIATED IMMUNITY; COMMON VARI-

ABLE IMMUNODEFICIENCY (CVID); COMPLEMENT CASCADE; IMMUNE DISORDERS; LIVING WITH IMMUNE DISORDERS; PARTIAL COMBINED IMMUNODEFICIENCY (PCID); SEVERE COMBINED IMMUNODEFICIENCY (SCID); T-CELL LYMPHOCYTE.

immunoglobulin A protein structure the IMMUNE SYSTEM produces. Immunoglobulins are the foundation molecules for the formation of antibodies. Immunoglobulins circulate in the BLOOD. The immunoglobulin's class designation reflects its molecular structure, which in turn dictates the action of the immunoglobulin. The five major classes of immunoglobulin provide different kinds of antibodies:

- Immunoglobulin A (IgA) is the main immunoglobulin in the body's secretions (tears, saliva, and mucus) and in colostrum, the first discharge from the mother's breasts after childbirth. It is the second most abundant immunoglobulin in the blood circulation. IgA boosts the IMMUNE RESPONSE capacity of the various MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT) structures. IgA blood levels decrease in lymphoblastic leukemias and increase in certain AUTOIMMUNE DISORDERS, notably RHEUMATOID ARTHRITIS and SYSTEMIC LUPUS ERYTHEMATOSUS (SLE).
- Immunoglobulin D (IgD) resides on the surface of the cell membrane of B-cell lymphocytes. Its primary role is to bind with antigens. IgD blood levels increase with chronic infections and certain myelomas.
- Immunoglobulin E (IgE) produces the antibodies responsible for HYPERSENSITIVITY REACTION as well as primary INFECTION-fighting antibodies. It also is the immune response's main defense against parasitic infection. IgE is the least abundant of the immunoglobulins in the blood circulation. Blood levels of IgE rise with hypersensitivity reactions.
- Immunoglobulin G (IgG) is the most abundant and versatile of the immunoglobulins. It makes up 75 percent of the immunoglobulin in the blood circulation. IgG binds with many types of leukocytes and activates the COMPLEMENT CASCADE. IgG is the only immunoglobulin that can cross the placental barrier between mother and fetus. IgG blood levels increase with infection and rheumatoid arthritis and decreases with lymphoblastic LEUKEMIA.
- Immunoglobulin M (IgM) is the third most abundant class of immunoglobulin in the blood circulation. The first contact with an ANTIGEN causes a B-CELL LYMPHOCYTE to produce IgM. IgM antibodies help collect cellular debris for more efficient PHAGOCYTOSIS. Blood levels of IgM increase with infectious mononucleosis, MALARIA, SLE, and rheumatoid arthritis.

Immunoglobulins collected from donated blood and PLASMA are blended to produce GAMMAGLOBULIN, a therapeutic form that boosts the nonspecific immune response.

For further discussion of immunoglobulins within the context of the structures and functions of the immune system, please see the overview section "The Immune System and Allergies."

See also ANTIBODY; ANTIBODY-MEDIATED IMMUNITY; LEUKOCYTE; LYMPHOCYTE; MONONUCLEOSIS, INFECTIOUS; VACCINE.

immunosenescence A decline in immune function and IMMUNE RESPONSE that occurs with aging. Researchers believe immunosenescence accounts for the increase in cancer and infections such as INFLUENZA and PNEUMONIA in people of old age. The decline occurs in both CELL-MEDIATED IMMUNITY (sometimes called cytotoxic immunity), in which T-cell lymphocytes attack and kill foreign antigens, and humoral immunity, in which B-cell lymphocytes generate the antibodies that circulate in the BLOOD. Though immunosenescence appears a normal physiologic process in that it happens to everyone as they grow older, researchers question whether it is an intrinsic function under genetic regulation or an extrinsic reaction to environmental factors, ranging from EATING HABITS to toxic exposure.

See also AGING, EFFECTS ON IMMUNE RESPONSE; ANTIBODY; ANTIGEN; APOPTOSIS; B-CELL LYMPHOCYTE; CELL STRUCTURE AND FUNCTION; LYMPHOCYTE; T-CELL LYMPHOCYTE.

immunosuppressive medications Drugs that limit or suppress some aspect of the IMMUNE RESPONSE. Immunosuppressive medications such as cyclosporine work by many different mechanisms

with the goal being to block the body's rejection of a transplanted organ or bone marrow and to prevent GRAFT VS. HOST DISEASE. Common immunosuppressive medications include

- CORTICOSTEROID MEDICATIONS, which inhibit the production of eosinophils, suppress the COMPLEMENT CASCADE, and block the activation of antibodies
- DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (DMARDS), which block the immune response in such of a way as to alter, at least temporarily, the course of the disease
- cytotoxic agents, which kill cells (cells that replicate rapidly, such as BLOOD cells, are more greatly affected)

Doctors prescribe immunosuppressive medications to treat AUTOIMMUNE DISORDERS, HYPERSENSITIVITY REACTION, and to prevent an immune response that targets a transplanted organ. Often doctors prescribe these medications in combination to quell the immune response on several fronts. This allows lower dosages for each type of medication, reducing the overall amount of medication the person must take and minimizing side effects. The approach also provides greater relief in severe presentations of chronic inflammatory diseases such as RHEUMATOID ARTHRITIS and SYSTEMIC LUPUS ERYTHEMATOSUS (SLE).

Immunosuppressive medications have numerous side effects, DRUG interactions, and risks specific to the medication. In general, the primary risk of immunosuppressive medications is INFECTION, particularly OPPORTUNISTIC INFECTION. Though doctors try to maintain a balance of immune suppression that controls symptoms yet allows the body to protect itself from infection, IMMUNOSUPPRESSIVE THERAPY opens the gateway for pathogens to invade. Aggressive antibiotic therapy then becomes necessary to eradicate the infection.

See also ANTIBIOTIC MEDICATIONS; ANTIHISTAMINE MEDICATIONS; CHEMOTHERAPY; DRUG INTERACTION; LIVING WITH IMMUNE DISORDERS; ORGAN TRANSPLANTATION; PATHOGEN.

immunosuppressive therapy Treatments that limit or suppress the IMMUNE RESPONSE. Such treatment may incorporate IMMUNOSUPPRESSIVE MEDICATIONS such as CORTICOSTEROID MEDICATIONS, DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS (DMARDS), CHEMOTHERAPY, RADIATION THERAPY, and MONOCLONAL ANTIBODIES (MABS).

Doctors may prescribe short-term immunosuppressive therapy (two to six weeks) to treat moderate to severe type I HYPERSENSITIVITY REACTION or to reduce INFLAMMATION due to injury. Long-term immunosuppressive therapy is generally a treatment option for chronic AUTOIMMUNE DISORDERS such as SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) and RHEUMATOID ARTHRITIS. People who have had organ transplants must take lifelong immunosuppressive therapy to reduce the risk for organ rejection and GRAFT VS. HOST DISEASE. The risk for complications and side effects rises the longer a person is on immunosuppressive therapy.

Immunoablation (the administration of high-DOSE chemotherapy or radiation therapy) wipes out the immune response altogether by killing the BONE MARROW, which removes all leukocytes and their subtypes from the IMMUNE SYSTEM's resource arsenal. This form of immunosuppressive therapy prepares the body to receive BONE MARROW TRANSPLANTATION or STEM CELL transplantation, which then rebuilds the immune system from the marrow up.

See also COMPLEMENT CASCADE; LEUKOCYTE; LIVING WITH IMMUNE DISORDERS; ORGAN TRANSPLANTATION; PROSTAGLANDINS.

immunotherapy The therapeutic use of biologic agents to manipulate the mechanisms of the IMMUNE SYSTEM. Immunotherapy, also called biologic response modification, is an effective method for reducing INFLAMMATION and other aspects of the IMMUNE RESPONSE to treat inflammatory AUTOIMMUNE DISORDERS such as RHEUMATOID ARTHRITIS. Immunotherapy is also a treatment option for many forms of cancer. The common types of immunotherapy are

- CYTOKINES such as INTERLEUKINS and INTERFERONS, which boost the cytotoxic (cell-killing) actions of T-cell lymphocytes and natural killer (NK) cells
- COLONY-STIMULATING FACTORS (CSFS), which stimulate the growth of leukocytes and lymphocytes (white BLOOD cells) in the BONE MARROW

- MONOCLONAL ANTIBODIES (MABS), which stimulate specific ANTIBODY activity

Vaccines are among the most effective and basic forms of immunotherapy. A VACCINE introduces a substance such as a VIRUS or strain of BACTERIA into the body at a level significant enough to stimulate an immune response yet mild enough to avoid establishing INFECTION in most people. Researchers are now exploring ways to apply the principles of vaccines to cancer treatment and CANCER PREVENTION. CANCER VACCINES, currently in investigational studies, attempt to modify the immune response by creating antibodies that will recognize the antigens on cancer cells should the cancer recur after initial treatment.

See also CANCER TREATMENT OPTIONS AND DECISIONS; GENE THERAPY; LEUKOCYTE; LYMPHOCYTE; NATURAL KILLER (NK) CELL; T-CELL LYMPHOCYTE; VACCINE.

inflammation The release of fluid (PLASMA) from the BLOOD vessels into the tissues, facilitating the movement of key immune proteins and other molecules to the site of injury or INFECTION. Inflammation is the mechanism of the IMMUNE RESPONSE for containing and mitigating whatever damage has occurred. PROSTAGLANDINS, which mast cells release, are the primary instigators of the inflammatory response. Inflammation occurs as a coupling of increased blood circulation to the area with increased capillary permeability (the amount of fluid the capillaries allow to escape into the spaces between cells). Though inflammation accompanies infection, it does not always indicate that an infective process is under way.

Plasma, the liquid portion of the blood, contains numerous immune elements, including antibodies, CYTOKINES, and complement factors. Swelling, which is the hallmark of inflammation, indicates that this mechanism is succeeding in getting the necessary immune elements to the site. IMMUNOGLOBULIN E (IgE) and certain of the cytokines are instrumental in the inflammation process. Inflammation typically causes swelling, PAIN, FEVER, and often redness of the SKIN at the site of the inflammation. When joints are inflamed, as in RHEUMATOID ARTHRITIS, the JOINT often feels stiff and has limited range of motion. TENDONITIS and BURSITIS are also common presentations of inflammation.

Treatment for inflammation is often NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS), DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (DMARDS), or CORTICOSTEROID MEDICATIONS, depending on the cause. When appropriate, ice to the local area provides relief from pain and helps contract the blood vessels to slow the flow of blood. The latter, in turn, reduces the amount of fluid that enters the tissues. Reducing use of the affected area facilitates HEALING and the body's reabsorption of the excess interstitial fluid, though movement to keep the joints from stiffening is also important. PHYSICAL THERAPY, TAI CHI, YOGA, and MASSAGE THERAPY are among the methods that help maintain mobility and FLEXIBILITY. Treatment also targets the circumstance causing the inflammation whenever possible, such as any underlying injury or condition.

For further discussion of inflammation within the context of the structures and functions of the immune system, please see the overview section "The Immune System and Allergies."

See also ANALGESIC MEDICATIONS; ANTIBODY; ANTIGEN; COMPLEMENT CASCADE; MAST CELL.

innate immunity The level of immune protection with which an individual is born. Researchers believe innate immunity, also called natural immunity, is the result of genetically encoded PATHOGEN recognition—that is, GENE-regulated ability to identify and mount an IMMUNE RESPONSE to neutralize certain BACTERIA, viruses, and other substances capable of causing INFECTION or otherwise doing harm to the body. The immune cell receptors recognize key characteristics of molecular structure common to many pathogens, called pathogen-associated molecular patterns (PAMPs), rather than specific pathogens. Their response does not require prior exposure before activation; thus PAMPs respond immediately to the presence of pathogens that fit the pattern. Innate immunity is species specific, which is why most infections cannot pass from one species to another. Pathogens capable of infecting multiple species are those that mutate for each species.

For further discussion of immunity within the context of the structures and functions of the

immune system, please see the overview section "The Immune System and Allergies."

See also ANTIBODY-MEDIATED IMMUNITY; CELL-MEDIATED IMMUNITY; VIRUS.

interferons CYTOKINES (molecules on the surface of cell membranes that direct cell activity) that block the activity of viruses and mediate numerous aspects of the IMMUNE RESPONSE. There are more than a dozen type 1 INTERFERONS, the most abundant of which are interferon-alpha and interferon-beta. B-cell lymphocytes and T-cell lymphocytes produce type 1 interferons, which primarily direct the functions of macrophages and natural killer (NK) cells in responding to viruses. Activated T-cells produce interferon-gamma, which is the only type 2 interferon. Interferon-gamma helps regulate INFLAMMATION.

Interferon-alpha and interferon-beta have strong tumor-suppression actions, which has led to their therapeutic use for certain kinds of cancer. Oncologists (doctors who specialize in treating cancer) administer recombinant forms of interferons (interferons that are synthesized in a laboratory using RECOMBINANT DNA technology) by injection to treat chronic myeloid LEUKEMIA, hairy cell leukemia, malignant melanoma, and some types of lymphoma. Doctors also use therapeutic interferons to treat HEPATITIS C and MULTIPLE SCLEROSIS. Pegylated interferons are synthesized to include polyethylene glycol, which delays the rate at which the body absorbs injected interferons.

See also B-CELL LYMPHOCYTE; CHEMOKINES; INTERLEUKINS; LYMPHOCYTE; LYMPHOKINES; MACROPHAGE; NATURAL KILLER (NK) CELL; T-CELL LYMPHOCYTE; VIRUS.

interleukins CYTOKINES that influence the growth, proliferation, and activity of leukocytes and other BLOOD cells. Leukocytes produce interleukins. There are 12 major interleukins, identified as interleukin 1 (IL-1) through IL-12. Among those significant to LEUKOCYTE development are

- IL-3, which influences blood stem cell differentiation into the various types of blood cells; leukocyte differentiation into granulocytes, monocytes, and lymphocytes; GRANULOCYTE differentiation into basophils; and LYMPHOCYTE differentiation into B-cell lymphocytes and T-cell lymphocytes
- IL-5, which influences leukocyte differentiation into eosinophils
- IL-7, which stimulates the BONE MARROW to produce lymphocytes

The interleukins also regulate the actions of leukocytes—monocytes, neutrophils, basophils, macrophages, B-cell lymphocytes, T-cell lymphocytes, natural killer (NK) cells, mast cells, PLASMA cells—in the IMMUNE RESPONSE, notably the INFLAMMATION process. The role of interleukins in the production and activity of basophils and neutrophils, the cells of the immune response largely responsible for inflammation, has come under scrutiny as a key factor in the development of conditions such as ATHEROSCLEROSIS. Research is under way to investigate methods to manipulate interleukin production and levels to reduce the inflammatory response in such circumstances, thus diminishing or eliminating the disease process. Other research is investigating therapeutic administration of interleukins to treat HIV/AIDS. Doctors currently use some synthesized interleukins therapeutically (notably IL-2) to treat certain types of cancer.

See also B-CELL LYMPHOCYTE; BLOOD STEM CELLS; INTERFERONS; LEUKOCYTE; MACROPHAGE; MAST CELL; MAJOR HISTOCOMPATIBILITY COMPLEX (MHC); MONOCYTE; NATURAL KILLER (NK) CELL; T-CELL LYMPHOCYTE.

leukotrienes Molecules that instigate INFLAMMATION during an IMMUNE RESPONSE. Mast cells secrete leukotrienes in response to stimulation by IMMUNOGLOBULIN E (IgE). Leukotrienes are derived from arachidonic acid, which is the same base source (precursor) as that of PROSTAGLANDINS, the other primary agents of inflammation. The actions of leukotrienes are most apparent in ASTHMA, in which they cause the bronchioles (tiny bronchi deep within the LUNGS) to constrict. Leukotriene release becomes more rapid with each HYPERSENSITIVITY REACTION. Leukotrienes also attract eosinophils, which cause swelling in the bronchial mucosa (mucous membrane lining of the bronchi). In inflammatory responses outside the pulmonary system, leukotrienes attract neutrophils with similar effect (swelling and discomfort). Eosinophils and neutrophils are types of granulocytes.

See also GRANULOCYTE; HISTAMINE; MAST CELL.

living with allergies About 50 million Americans live with allergies—to pollens, animal danders, latex, fragrances, foods, drugs, and other substances—that cause them to alter their lifestyles. Most people can reduce exposure to allergens enough to lessen symptoms.

Outdoor Allergens

The primary outdoor allergens are pollens and molds. Pollen is the powdery and often microscopic granules that are the male cells of plants. The plant disperses pollen into the air, which carries it to other plants. The dusting of pollen on plants of the same species fertilizes them, permitting them to propagate. The pollens most likely to cause a HYPERSENSITIVITY REACTION are grasses and trees. Tree pollens are highest in early spring and grass pollens (including weeds) are highest in early summer. Both tree and grass pollens remain high through summer and into early autumn in most regions of the United States. Molds are also microscopic, airborne substances, though correlate to weather conditions rather than seasons. Molds are highest when the weather is cool and wet. Raking leaves in the autumn is a major risk for exposure to molds.

Many weather reports include local pollen counts and mold counts. Counts that are moderate to high are likely to cause ALLERGY symptoms in people who are allergic; very high counts may cause symptoms in people who do not typically have seasonal allergies. Because pollens and molds are airborne, it is difficult to escape them. Allergists recommend ANTIHISTAMINE MEDICATIONS or DESENSITIZATION to mitigate symptoms. Staying indoors is not usually an effective or practical strategy.

Steps that may help include taking off outdoor clothing immediately upon coming indoors and washing the face, arms, hands, and other exposed areas with soap and water (showering is best). Washing the hands especially helps limit spreading pollen to the NOSE and EYE via contact. Some people can reduce their symptoms by wearing a mask over the face and nose during outdoor activities when pollen and mold counts are high. As well, pollen counts are highest in the early morning. Central air-conditioning in the home and in the car helps filter pollens and other particulates.

Being outdoors brings the risk of exposure to other allergens as well. People who are allergic to the sting of bees and wasps have a high risk of exposure during spring and summer when plants are in bloom. Wasps and related stinging insects become active in the autumn, especially in

wooded areas or areas where there is mud. Contact with poison ivy, poison oak, or poison sumac can cause symptoms any time of the year, though this is more of a problem in spring and summer.

Indoor Allergens

Indoor allergens are commonly dust, insect droppings, and pet dander. Cockroach droppings are the prime cause of ALLERGIC ASTHMA in urban areas, especially in children. Cockroaches are attracted to moisture and food debris; keeping living areas dry and clean reduces the attraction. Dust mite droppings are also a significant cause of allergic ASTHMA and ALLERGIC RHINITIS. Dust mites also prefer humid environments, though their food source is the microscopic flakes of SKIN that people continually shed. These flakes accumulate in bedclothes and bed linens especially. Keeping the bedroom dry and washing sheets once a week in hot water helps reduce the dust mite population.

About 80 percent of American households have pets. About the same percentage of people who have allergies are allergic to pet dander (most often cat dander). Some studies have found animal dander is as pervasive in the indoor environment as is pollen in the outdoor environment. Desensitization is the recommendation of most allergists for people who are allergic but want to have pets. Though desensitization may take three to five years to become fully effective, it is a permanent solution. There are no pets that are "low allergy." The length of an animal's coat has little relationship to its ability to evoke an allergic reaction. Other measures include washing the hands and changing the clothes after handling an animal, and keeping pets out of the bedroom.

Central heating and air-conditioning are effective for controlling humidity as well as filtering the air. Central vacuum systems are also helpful because they deposit vacuumed debris outside the living area, usually into a container in the garage or basement. High-efficiency particulate air (HEPA) filters can remove many kinds of allergens from the air.

See also ALLERGEN; ALLERGY TESTING; QUALITY OF LIFE.

living with immune disorders Living with an immune disorder requires special attention to circumstances that increase the risk for INFECTION. IMMUNE DISORDERS increase susceptibility to infection either as a direct result of the disease process or, in AUTOIMMUNE DISORDERS, as a consequence of the medications necessary to keep symptoms in check. The most important factor for controlling the symptoms of immune disorders is taking medications as prescribed. Immune function is complex, and often the therapeutic approach combines different kinds of medications to achieve an overall balance to the best extent possible within the parameters of the disease process. Though many complementary approaches are beneficial, some may interfere with conventional treatments and medications.

Nutritious EATING HABITS and regular physical activity benefit the IMMUNE SYSTEM in innumerable ways. The appropriate NUTRIENTS give the body the building blocks—amino acids—it needs to make the components of the IMMUNE RESPONSE. Autoimmune conditions may restrict physical activity, yet physical activity helps maintain optimal function. PHYSICAL THERAPY and MASSAGE THERAPY are conventional means for improving range of motion, STRENGTH, and FLEXIBILITY. YOGA, TAI CHI, and qi gong are alternative approaches that can do the same, along with MEDITATION to help relieve stress and improve mental clarity and focus. BIOFEEDBACK and HYPNOSIS are other methods to manage symptoms and establish a sense of control or peaceful coexistence with the condition. Numerous studies suggest a surprisingly intricate relationship between stress, emotion, and immune function, making stress management particularly important with chronic immune dysfunction.

Efforts to prevent the chronic infections that often accompany immune disorders or the use of IMMUNOSUPPRESSIVE MEDICATIONS to treat autoimmune disorders include limiting exposure to other people who are sick (such as during cold and flu season). Frequent HAND WASHING is an effective means for containing pathogens.

See also LIVING WITH ALLERGIES; HYPERSENSITIVITY REACTION; PATHOGEN; PSYCHONEUROIMMUNOLOGY; QUALITY OF LIFE; STRESS AND STRESS MANAGEMENT.

lymphokines CYTOKINES that convey biochemical messages among lymphocytes (a type of white

BLOOD cell) to direct their actions during an IMMUNE RESPONSE. B-cell lymphocytes and T-cell lymphocytes both secrete lymphokines. Lymphokines activate and coordinate numerous immune functions across the spectrum of the immune response. They also stimulate cell growth and activation and stimulate MACROPHAGE activity.

See also B-CELL LYMPHOCYTE; COMPLEMENT CASCADE; INTERFERONS; INTERLEUKINS; LEUKOCYTE; LYMPHOCYTE; MONOKINES; T-CELL LYMPHOCYTE.

M

macrophage A MONOCYTE that leaves the BLOOD circulation and takes up residence in the tissues. Once there, the cell undergoes several changes:

- It greatly enlarges.
- It develops pseudopods (footlike projections) that permit it to move through tissue.
- It increases the amount of lysozyme its granules contain, increasing its ability to consume cellular debris.

Macrophages, the IMMUNE SYSTEM's tissue-based scavengers, are part of the MONONUCLEAR PHAGOCYTE SYSTEM. They engulf, dismantle, and consume the carcasses of cells that other immune cells destroy and of cells that die naturally (APOPTOSIS). They also absorb and breakdown the particulate debris from toxins, BACTERIA, viruses, and other substances. Macrophages also respond to the inflammatory process, contributing to INFLAMMATION and the formation of granulomas. As well, macrophages are key to ANTIGEN presentation and processing, the mechanism by which T-cell lymphocytes and B-cell lymphocytes recognize nonself antigens. As the macrophage dismantles a substance, it displays the substance's antigens, along with the relevant MAJOR HISTOCOMPATIBILITY COMPLEX (MHC), on the surface of its cell membrane for lymphocytes to detect. Lymphocytes ignore debris that belongs to the body. Debris that is foreign activates an IMMUNE RESPONSE.

For further discussion of macrophages within the context of the structures and functions of the immune system, please see the overview section "The Immune System and Allergies."

See also B-CELL LYMPHOCYTE; GRANULOMA; LYMPHOCYTE; NATURAL KILLER (NK) CELL; T-CELL LYMPHOCYTE; VIRUS.

major histocompatability complex (MHC) The group of genes, located on CHROMOSOME 6, that determine the HUMAN LEUKOCYTE ANTIGENS (HLAS) the body's cells carry on their cell membranes. HLAs are unique proteins that cell membranes display to identify themselves to the IMMUNE SYSTEM. There are three types of MHC:

- Class I MHC encodes the HLAs that all nucleated cells and platelets in the body carry to identify them as self cells (the body's own cells).
- Class II MHC encodes the HLAs that lymphocytes, macrophages, dendritic cells, and other substances involved in ANTIGEN processing carry. These HLAs are fundamental to ANTIBODY-MEDIATED IMMUNITY and are also responsible for GRAFT VS. HOST DISEASE and organ rejection in people who undergo ORGAN TRANSPLANTATION.
- Class III MHC encodes the immunoglobulins from which the immune system forms antibodies.

MHC is central to antigen processing. When a MACROPHAGE or dendritic cell (phagocytes, also called scavenger cells, in the MONONUCLEAR PHAGOCYTE SYSTEM) consumes cellular debris, it displays the antigens of the debris alongside its own HLA. This comparison display allows T-cell lymphocytes to recognize the cellular debris as self or nonself and respond accordingly. Self antigen evokes no reaction; nonself antigen mobilizes the IMMUNE RESPONSE.

See also ANTIBODY; CELL-MEDIATED IMMUNITY; COMPLEMENT CASCADE; GENE; IMMUNOGLOBULIN; LYMPHOCYTE; MACROPHAGE; PHAGOCYTE; PHAGOCYTOSIS; PLATELET; T-CELL LYMPHOCYTE.

mast cell A granulated LEUKOCYTE that resides in tissues throughout the body. When the IMMUNE RESPONSE stimulates mast cells, they release PROSTAGLANDINS, HISTAMINE, and other biochemicals from their granules. Mast cells are primarily responsible for the symptoms that are the hallmark of the HYPERSENSITIVITY REACTION: INFLAMMATION, itching, SKIN RASH, coughing, and sneezing. Mast cells have an abundant presence in the tissues of mucous membranes such as the NOSE, pulmonary tract (TRACHEA and bronchi), and gastrointestinal tract. Mast cells also infiltrate the connective tissues. They respond to the stimulation of complement factors and to IMMUNOGLOBULIN E (IgE) antibodies.

For further discussion of mast cells within the context of the structures and functions of the immune system, please see the overview section "The Immune System and Allergies."

See also ANTIBODY; COMPLEMENT CASCADE; COUGH; LIVING WITH ALLERGIES; MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT); SNEEZE.

monoclonal antibodies (MAbs) Antibodies produced in a laboratory using RECOMBINANT DNA technology. MAbs derive from cloned mouse SPLEEN cells (hence the designation "monoclonal") containing the desired ANTIBODY fused with human myeloma cells. Mouse cells have proteins very similar to the proteins of human cells. Human myeloma cells, because they are cancer cells, have the ability to replicate without limitation. The myeloma cells arise from B-cell lymphocytes, which produce antibodies.

When scientists fuse the two cells together, they achieve cells (called hybridomas) that combine the desired ANTIGEN sensitization with the ability to endlessly replicate antibody-producing cells. After fusion, scientists can attach radioactive molecules for diagnostic imaging or to deliver fatal radiation to specific cells (called conjugated MAbs). Doctors then can inject MAbs into people to stimulate the IMMUNE RESPONSE as a mechanism for fighting INFLAMMATION (such as in RHEUMATOID ARTHRITIS) and certain types of cancer or to specifically target certain cells for death without affecting other cells. Indiscriminate cell death is a significant limitation of current CHEMOTHERAPY.

A key limitation of therapeutic MAbs is that the body recognizes them as nonself and configures antibodies against them. MAbs are highly effective for the first treatment, then may be less effective or initiate a HYPERSENSITIVITY REACTION in subsequent treatment efforts.

THERAPEUTIC MONOCLONAL ANTIBODIES (MABS)

abciximab (ReoPro)	alemtuzumab (MAb Campath)
bevacizumab (Avastin)	cetuximab (Erbitux)
daclizumab (Zenapax)	infliximab (Remicade)
lym-1 (Oncolym)	muromonab-CD3 (OKT3)
omalizumab (Xolair)	rituximab (Rituxan)
tositumomab (Bexxar)	trastuzumab (Herceptin)

For further discussion of MAbs within the context of the structures and functions of the immune system, please see the overview section "The Immune System and Allergies."

See also B-CELL LYMPHOCYTE; CANCER TREATMENT OPTIONS AND DECISIONS; IMMUNOTHERAPY; INTERFERONS; INTERLEUKINS; MOLECULARLY TARGETED THERAPIES.

monokines CYTOKINES that convey biochemical messages among monocytes (white BLOOD cells in the blood circulation) and macrophages (white blood cells that reside in the tissues). Monokines direct the actions of these immune cells during the IMMUNE RESPONSE, stimulating and coordinating numerous functions. There is some overlap between monokines and LYMPHOKINES (which lymphocytes produce).

See also COMPLEMENT CASCADE; IMMUNE SYSTEM; INTERFERONS; INTERLEUKINS; LEUKOCYTE; LYMPHOCYTE; MACROPHAGE; MONOCYTE.

mononuclear phagocyte system The combined activity of the IMMUNE SYSTEM's phagocytes—monocytes in the BLOOD circulation and macrophages in the tissues—to consume cellular debris. These cells are scavengers within the body, responsible for cleaning up after B-cell lymphocytes, T-cell lymphocytes, and natural killer (NK) cells. They also clear the debris that results from normal cell death (APOPTOSIS). They are called mononuclear because their cell structure contains a single nucleus; neutrophils, which are also phagocytes, have multiple nuclei (and are called polymorphonuclear). The COMPLEMENT CASCADE (an interaction of proteins or

factors that begins with ANTIBODY–ANTIGEN binding) is the primary alert mechanism that activates the mononuclear phagocyte system. Monocytes and macrophages work in a coordinated fashion, communicating via CYTOKINES (cell-originated biochemical messages) with other cells involved in the IMMUNE RESPONSE.

For further discussion of the mononuclear phagocyte system within the context of the structures and functions of the immune system, please see the overview section "The Immune System and Allergies."

See also B-CELL LYMPHOCYTE; CELL STRUCTURE AND FUNCTION; GENE; GRANULOCYTE; MACROPHAGE; MONOCYTE; NATURAL KILLER (NK) CELL; PHAGOCYTE; PHAGOCYTOSIS; T-CELL LYMPHOCYTE.

mucosa-associated lymphoid tissue (MALT) A loosely organized collection of LYMPH tissue that underlies and integrates with epithelial tissue (the lining of mucous membranes) throughout the body. MALT reinforces the body's immune presence and response in areas of the body that provide direct interface with the external environment. These areas, such as the gastrointestinal tract and the LUNGS, are most vulnerable to breaches that could allow pathogens to enter the body to cause INFECTION.

MALT contains clusters of phagocytic cells such as macrophages and dendritic cells, which consume cellular debris, as well as T-cell lymphocytes and B-cell lymphocytes. T-cell lymphocytes attack and kill invading pathogens, and B-cell lymphocytes produce antibodies to protect against future invasion by the same pathogens. There are several types of MALT; each has specific functions, according to its location in the body. Among them are

- BRONCHUS-ASSOCIATED LYMPHOID TISSUE (BALT), which strengthens the body's defense against INFLUENZA and PNEUMONIA
- GUT-ASSOCIATED LYMPHOID TISSUE (GALT), which helps protect against invasion by gastrointestinal viruses
- NOSE-ASSOCIATED LYMPHOID TISSUE (NALT), which intensifies the body's resistance to airborne viruses such as those that cause COLDS
- SKIN-ASSOCIATED LYMPHOID TISSUE (SALT), which helps block BACTERIA, fungi, and other pathogens from passing through microscopic breaks in the SKIN
- VASCULAR-ASSOCIATED LYMPHOID TISSUE (VALT), which infiltrates the epithelium of the BLOOD vessels

MALT may be the site of solid tumors that develop in LYMPHOMA (sometimes called MALT lymphoma). The most common MALT site for such an occurrence is the gastrointestinal tract. Researchers believe these lymphomas develop when a constant assault, such as a persistent infection, engages the MALT site. B-cell lymphocytes accumulate to fight the infection. When their accumulation persists over time, which is abnormal, the B-cell lymphocytes turn cancerous. The connection with MALT lymphomas that arise from GALT is *HELICOBACTER PYLORI* infection, which also has a strong connection to STOMACH CANCER. Researchers believe *H. pylori* may account for 85 percent or more of gastrointestinal MALT lymphomas, many of which grow in the STOMACH. Treatment is highly successful when the diagnosis of MALT lymphoma occurs early in the CANCER's development because the tumors grow slowly and lack aggression in spreading.

For further discussion of MALT within the context of the structures and functions of the immune system, please see the overview section "The Immune System and Allergies."

See also ANTIBODY; B-CELL LYMPHOCYTE; FUNGUS; LYMPHOCYTE; MACROPHAGE; METASTASIS; MONONUCLEAR PHAGOCYTE SYSTEM; PATHOGEN; PHAGOCYTE; PHAGOCYTOSIS; T-CELL LYMPHOCYTE; VIRUS.

multiple chemical sensitivity syndrome A constellation of symptoms that result from exposure to common chemicals at levels that do not normally cause response or reaction. Multiple chemical sensitivity syndrome is difficult to diagnose and treat. Symptoms are often broad ranging. There remains disagreement among medical experts (doctors and researchers) about the diagnostic criteria and causes of the syndrome. Some believe multiple chemical sensitivity syndrome is a component of GENERALIZED ANXIETY DISORDER (GAD)

or PANIC DISORDER. Others believe it is a HYPERSENSITIVITY REACTION. Symptoms of multiple chemical sensitivity syndrome often include

- PALPITATIONS and CHEST PAIN
- fatigue and shortness of breath (DYSPNEA)
- difficulty sleeping
- cognitive disturbances

The diagnostic path is primarily clinical, based on the person's symptoms. Though BLOOD tests can detect changes in immune indicators such as IMMUNOGLOBULIN levels, LEUKOCYTE activity, and complement factors, the changes are inconsistent from one person to the next and do not necessarily correlate either to symptoms or exposures.

Treatment is avoidance, whenever possible, of environments and circumstances that exacerbate symptoms. Because the substances and their quantities or exposures to them are common, however, it is often hard for the person to avoid exposure. Medications typically given to treat hypersensitivity reactions, such as ANTIHISTAMINE MEDICATIONS or CORTICOSTEROID MEDICATIONS, do not relieve the symptoms and discomforts of multiple chemical sensitivity syndrome. For most people the syndrome is chronic, with symptoms waxing and waning. Multiple chemical sensitivity syndrome can have a significant affect on QUALITY OF LIFE.

See also CHRONIC FATIGUE SYNDROME; COGNITIVE FUNCTION AND DYSFUNCTION; COMPLEMENT CASCADE; FIBROMYALGIA.

N

natural killer (NK) cell A granular LYMPHOCYTE (white BLOOD cell with granules in its cytoplasm) that has cytotoxic (cell-killing) functions within the IMMUNE RESPONSE. NK cells belong to the CELL-MEDIATED IMMUNITY pathway of the immune response and do not require ANTIGEN presentation to target a cell for destruction. NK cells are particularly involved in killing tumor cells. They release molecules that puncture or perforate (make molecular holes in) the cell membrane of the cell under attack. This assault may directly kill the cell or cause accelerated APOPTOSIS (planned cell death) that the target cell itself initiates in response to the damage it experiences.

For further discussion of natural killer cells within the context of the structures and functions of the immune system, please see the overview section "The Immune System and Allergies."

See also ANTIBODY-MEDIATED IMMUNITY; B-CELL LYMPHOCYTE; MACROPHAGE; T-CELL LYMPHOCYTE.

nonsteroidal anti-inflammatory drugs (NSAIDs) Medications that relieve INFLAMMATION by suppressing the action of PROSTAGLANDINS, which are responsible for the inflammatory response. There are several types of prostaglandins, most of which are biochemical messengers that have numerous roles in routine cellular activity. Other prostaglandins are the agents of inflammation. The prostaglandins that incite inflammation do so by summoning numerous other biochemicals to the site of an injury, ultimately resulting in fluid accumulation and swelling at the site.

Three NSAIDs are available in over-the-counter (OTC) preparations as well as stronger prescription-only products: ibuprofen, naproxen, and ketoprofen. All other NSAIDs available in the United States (except aspirin) require a doctor's prescription.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)	
aspirin	diclofenac
diflunisal	etodolac
fenoprofen	flurbiprofen
ibuprofen	indomethacin
ketoprofen	meclofenamate
mefenamic acid	meloxicam
naproxen	oxaprozin
nabumetone	piroxicam
sulindac	tolmetin

How These Medications Work

NSAIDs work by blocking the action of cyclooxygenase (COX), the enzyme that allows cells to convert arachidonic acid (a dietary fatty acid found in meats) into prostaglandins. The two main forms of COX are cyclooxygenase 1 (COX-1) and COX-2. Many types of cells in the body contain COX-1, but COX-2 occurs primarily in mast cells. COX-1 is responsible for prostaglandin synthesis for these roles. Prostaglandins are also the agents of inflammation. Mast cells contain COX-2, which enables them to synthesize large quantities of prostaglandins during an IMMUNE RESPONSE.

Most NSAIDs are nonselective; they block both COX-1 and COX-2. Though this action effectively relieves inflammation and associated symptoms (such as PAIN and FEVER), it also interferes with various general functions of cells throughout the body. One consequence of this interference is STOMACH upset. Gastric cells contain an abundance of COX-1 and synthesize forms of prostaglandin that help protect the lining of the stomach. Suppressing COX-1 activity reduces this protection. As

well, the NSAID preparations are generally acids, which further irritate stomach tissues.

Therapeutic Applications

Doctors prescribe or recommend NSAIDs for pain relief and to reduce fever and inflammation, such as from musculoskeletal injuries. NSAIDs have widespread therapeutic applications and are among the most commonly used medications in the United States. Though all NSAIDs share the same mechanism of action, some are more effective for specific conditions. Ibuprofen, naproxen, and ketoprofen are effective for general relief. Other NSAIDs more aggressively block COX, making them especially useful for moderate OSTEOARTHRITIS, RHEUMATOID ARTHRITIS, and inflammatory disorders such as SYSTEMIC LUPUS ERYTHEMATOSUS (SLE).

The original NSAID is aspirin, first isolated and used as a therapeutic preparation in the late 1800s. Aspirin, a nonselective COX inhibitor, remains the most commonly used medication in the world, primarily for its ability to relieve pain and fever. In the 1970s cardiologists began recommending daily aspirin for people at high risk for HEART ATTACK. During an inflammatory response prostaglandins combine with other substances to make the surfaces of platelets (clotting cells) sticky. This encourages PLATELET AGGREGATION, the first step of COAGULATION (clot formation). Blocking prostaglandin synthesis reduces the likelihood for BLOOD clots to form in the blood vessels. This effect is unique to aspirin among the NSAIDs; other NSAIDs have only very mild antiplatelet effect.

In the late 1990s and early 2000s several selective COX-2 NSAIDs became available. These COX-2 inhibitors had the ability to selectively target and block only COX-2, allowing COX-1-mediated prostaglandin synthesis to continue unimpeded while preventing COX-2-mediated synthesis to reduce inflammation. However, widespread use of COX-2 inhibitors revealed that these medications carried increased risk for heart attack, and several were withdrawn from the US market. Nonselective (classic) NSAIDs do not appear to carry the same risk, though may increase the risk for heart attack in people who have recently had OPEN HEART SURGERY.

People who have recently had OPEN HEART SURGERY or HEART ATTACK should check with their doctors before taking any nonsteroidal anti-inflammatory drug (NSAID) preparation, including cold and flu products that contain an NSAID.

Risks and Side Effects

The most common risk of NSAIDs is gastric upset and PEPTIC ULCER DISEASE. Extended use of an NSAID diminishes the amount of prostaglandins in the stomach, reducing the ability of the gastric mucosa (stomach lining) to protect itself from the acid normally present in the stomach as well as the acid of the NSAID itself. Some NSAIDs have more of this affect. Other common side effects include allergic reaction and interaction with other drugs. NSAIDs interact with numerous drugs as well as with each other. TINNITUS (ringing in the ears) is an early indication of excessive NSAID consumption. Long-term, high-DOSE NSAID use can cause permanent kidney and LIVER damage and failure of these organs.

See also ASPIRIN THERAPY; CORTICOSTEROID MEDICATIONS; DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (DMARDS); DRUG INTERACTION; EAR; IMMUNOSUPPRESSIVE MEDICATIONS; KIDNEYS; LIVER FAILURE; MAST CELL; PLATELET; RENAL FAILURE.

nose-associated lymphoid tissue (NALT)

Loosely organized collections of LYMPH tissue embedded in the mucous membrane lining (mucosa) of the nasal passages and sinus cavities. Nasal mucous, which the nasal mucosa secretes, is one of the body's front-line protective mechanisms, providing a physical barrier that repels or traps foreign substances such as BACTERIA, viruses, toxins, and inhaled particles. Many pathogens gain entry to the body through the NOSE. NALT contains numerous B-cell lymphocytes and T-cell lymphocytes that detect and respond to invading pathogens. Macrophages, eosinophils, and other phagocytic cells are also concentrated in NALT to clean up cellular debris that NALT traps or collects.

The mucous membrane lining of the nose is the first point of contact for inhaled allergens. Its mast

cells quickly initiate an IMMUNE RESPONSE by releasing HISTAMINE and other biochemicals to stimulate LYMPHOCYTE activity. This HYPERSENSITIVITY REACTION results in the common symptoms of ALLERGIC RHINITIS (seasonal allergies). In 2003 the US Food and Drug Administration (FDA) approved the first nasal VACCINE for INFLUENZA (the flu). It was the first to capitalize on the immune response NALT can generate to provide systemic (bodywide) IMMUNITY for the influenza strains the vaccine contains.

For further discussion of NALT within the context of the structures and functions of the immune system, please see the overview section "The Immune System and Allergies."

See also ALLERGEN; B-CELL LYMPHOCYTE; BRONCHUS-ASSOCIATED LYMPHOID TISSUE (BALT); COLDS; MACROPHAGE; MAST CELL; MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT); PATHOGEN; PHAGOCYTE; SKIN-ASSOCIATED LYMPHOID TISSUE (SALT); SNEEZE; VASCULAR-ASSOCIATED LYMPHOID TISSUE (VALT); VIRUS.

P–R

partial combined immunodeficiency (PCID) An immune disorder in which the IMMUNE SYSTEM is missing key components. Most often people who have PCID lack certain leukocytes (white BLOOD cells), which impairs their ability to form antibodies (develop IMMUNITY) and fight INFECTION. The abnormality might be with cell differentiation, maturity, or function. Sometimes PCID involves deficits of complement factors, the specialized proteins that activate ANTIBODY–ANTIGEN binding. Symptoms of PCID vary somewhat, depending on the immune deficit though generally include frequent infections and autoimmune reactions. Common infections are PNEUMONIA and CANDIDIASIS (thrush). OPPORTUNISTIC INFECTION may also occur. Autoimmune reactions often involve the SKIN, appearing as atopic DERMATITIS and other rashes.

The diagnostic path typically includes blood tests that measure the types and quantities of white blood cells, IMMUNOGLOBULIN, and complement factors. GENETIC TESTING may identify the presence of GENETIC DISORDERS that have IMMUNODEFICIENCY components. Treatment varies according to the immunodeficiency and severity of symptoms, though usually includes ANTIBIOTIC MEDICATIONS to control infections and GAMMAGLOBULIN injections to bolster the IMMUNE RESPONSE.

See also ANTIBODY-MEDIATED IMMUNITY; CELL-MEDIATED IMMUNITY; COMMON VARIABLE IMMUNODEFICIENCY (CVID); COMPLEMENT CASCADE; IMMUNE DISORDERS; LEUKOCYTE; LIVING WITH IMMUNE DISORDERS; RASH; SEVERE COMBINED IMMUNODEFICIENCY (SCID).

passive immunity IMMUNITY (protection from INFECTION) that occurs without activation of the IMMUNE RESPONSE. A newborn has passive immunity from the antibodies in his or her mother's BLOOD at the time of birth and continues to receive limited ANTIBODY protection for the duration of BREASTFEEDING. Passive immunity also occurs when a person receives GAMMAGLOBULIN that contains antibodies present in the blood (PLASMA) of the donors who are the source for the gammaglobulin.

For further discussion of immunity within the context of the structures and functions of the immune system, please see the overview section "The Immune System and Allergies."

See also ACTIVE IMMUNITY; INNATE IMMUNITY.

Peyer's patches Small, nodular clusters of lymphoid tissue scattered throughout the mucous membrane lining of the SMALL INTESTINE. Though not encapsulated as are LYMPH NODES, Peyer's patches are more distinct and organized than other MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT). Peyer's patches are elements of GUT-ASSOCIATED LYMPHOID TISSUE (GALT), a subset of MALT. GALT lies beneath the epithelial tissue (mucosal lining) of the gastrointestinal tract. Peyer's patches contain concentrations of B-cell lymphocytes that actively produce antibodies. They also contain some T-cell lymphocytes and phagocytic cells to enhance the IMMUNE RESPONSE in the small intestine.

For further discussion of Peyer's patches within the context of the structures and functions of the immune system, please see the overview section "The Immune System and Allergies."

See also ANTIBODY; B-CELL LYMPHOCYTE; LYMPHOCYTE; PHAGOCYTE; T-CELL LYMPHOCYTE.

prostaglandins A large family of fast-acting lipid mediators primarily responsible for initiating INFLAMMATION, FEVER, and PAIN during the IMMUNE RESPONSE. Prostaglandins are also vital for numerous functions throughout the body. Thromboxane, one of the prostaglandins, facilitates PLATELET

AGGREGATION to aid COAGULATION (BLOOD clotting). Other prostaglandins facilitate calcium transport to and from cells, the onset and progression of labor during CHILDBIRTH, and the functions of other hormones. Prostaglandins are also responsible for discomforts related to their release, such as after injury when inflammation results or when menstrual cramps (DYSMENORRHEA) occur.

Prostaglandin activity is autocrine (affects only cells that secrete it) or paracrine (affects cells within immediate proximity of the secreting cells). Prostaglandin activity is also intense but short lived, though the symptoms of the resulting inflammation continue for some time after prostaglandin release stops. Mast cells are the main source of prostaglandin synthesis and secretion. Epithelial cells (surface cells of the SKIN and mucous membranes) and platelets also produce as well as respond to prostaglandins.

PROSTAGLANDINS AND THE PROSTATE GLAND

The researchers who discovered prostaglandins in the 1930s isolated the first member of this biochemical family from SEMEN—the secretions of the PROSTATE GLAND. They named it for this connection. Over the following decades further research identified a number of prostaglandins and determined that nearly every cell in the body contains some form of prostaglandin. Aspirin was the first DRUG to block the synthesis of prostaglandins.

The enzymes cyclooxygenase 1 (COX-1) and COX-2 facilitate the synthesis of prostaglandins from arachidonic acid, an essential fatty acid (a fatty acid the body requires for health but cannot synthesize from other substances so must obtain from dietary sources) found in red meats and peanuts. Arachidonic acid is also the foundation for LEUKOTRIENES, other biochemicals also involved in the inflammatory response. The enzyme lipoxygenase facilitates the conversion of arachidonic acid to leukotrienes. COX-1 is primarily in the STOMACH, KIDNEYS, and walls of the blood vessels; it maintains the prostaglandins necessary for the body's normal functioning. COX-2 is present in the tissues and becomes active during an inflammatory response.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS), including aspirin, block the action of COX, preventing prostaglandin production. This action provides pain relief, reduces fever, and mitigates the swelling associated with inflammation. Though much therapeutic focus is on blocking prostaglandin production, there are numerous therapeutic applications for synthetic prostaglandins. Therapeutic administration of synthetic prosta-glandin E_1 (PGE_1) maintains a patent ductus arteriosus in infants born with serious congenital heart defects. Prostaglandin E_2 (PGE_2) and prostaglandin F_2 (PGF_2) cause the UTERUS to contract, either initiating or strengthening labor.

See also CONGENITAL HEART DISEASE; CRAMP; HORMONE; IMMUNE RESPONSE; IMMUNOGLOBULIN; MAST CELL; PLATELET.

psychoneuroimmunology The interrelationships between emotions, neurologic function, and the IMMUNE SYSTEM. In the 1970s researchers discovered receptors for neuropeptides on cells throughout the body, including the immune system. The BRAIN produces neuropeptides, protein-based structures that convey biochemical messages related to cognition (thought and logic) and emotion. Neuropeptides include endorphins and enkephalins, substances connected to perceptions of SATIETY and pleasure.

Though researchers do not yet understand how neuropeptides affect IMMUNE RESPONSE, they do know emotional stress affects physical health. They also know that the immune system affects neurologic functions, which is one reason people feel irritable and cranky when they are sick. It appears that the primary messengers for immune-to-neural communication are the CYTOKINES immune cells produce during the immune response, notably INTERLEUKINS, which are capable of activating NERVE impulses that convey signals to the brain. Researchers continue to explore ways to use these connections for health, HEALING, and disease prevention.

See also MIND–BODY CONNECTION.

reticuloendothelial system See MONONUCLEAR PHAGOCYTE SYSTEM.

rheumatoid arthritis A chronic, autoimmune disorder in which nodules and INFLAMMATION develop within the synovial capsules of the joints, causing erosion of the BONE and connective tissues, eventually deforming the JOINT. Synovial membranes encapsulate the joints and secrete synovial fluid, which lubricates the structures of the joint so they move smoothly and freely against each other. The antibodies that characterize rheumatoid arthritis attack the cells of the synovial membrane, causing inflammation and an IMMUNE RESPONSE that treats the cells as though they were invaders. The repeated inflammation over time results in fibrosis (scarring) that destroys the ability of the cells to produce synovial fluid and constricts the movement of the joint.

About two million Americans have rheumatoid arthritis, two thirds of them women. Rheumatoid arthritis most commonly develops between the ages of 20 and 50, though can occur in children (juvenile rheumatoid arthritis). Although treatments and lifestyle strategies can reduce inflammation and relieve symptoms, at present there is no cure for rheumatoid arthritis.

IS IT RHEUMATOID ARTHRITIS OR OSTEOARTHRITIS?

Arthritis is any condition of INFLAMMATION that affects the joints. OSTEOARTHRITIS is the form most people identify; about 20 million Americans have osteoarthritis. Though both forms involve inflammation of the joints, the two conditions are quite different. In osteoarthritis inflammation occurs in response to damage, usually that of repeated wear and tear, within the joints. In rheumatoid arthritis, the inflammation occurs first as a malfunction of the IMMUNE RESPONSE and causes damage to the joints. Osteoarthritis is more common in people over age 65, whereas rheumatoid arthritis usually arises before age 50.

Symptoms and Diagnostic Path

The symptoms of rheumatoid arthritis typically include

- PAIN and swelling in the joints, especially the small joints of the hands and fingers
- stiffness in the joints, especially upon awakening or after long periods of inactivity
- low-grade FEVER
- fatigue and weakness
- rheumatoid nodules, painless bumps under the SKIN that develop at pressure points
- joint deformity as the disease progresses

The diagnostic path includes BLOOD tests to detect antibodies and other indications of inflammation. Many people who have rheumatoid arthritis have a specific ANTIBODY called rheumatoid factor, though not all people who have rheumatoid arthritis have this antibody, and conversely, rheumatoid factor may be present in people who do not have rheumatoid arthritis. Blood levels of C-REACTIVE PROTEIN also can indicate whether inflammation exists in the body. X-rays can help the doctor evaluate and monitor damage to the joints and bones.

Treatment Options and Outlook

Treatment typically blends lifestyle measures to protect affected joints from undue stress and medications to relieve inflammation and pain. Daily exercise and activity that puts each affected joint through its complete range of motion help keep SCAR tissue from contracting (tightening) within the synovial capsule, maintaining relative freedom of movement. Activities such as YOGA and TAI CHI also improve FLEXIBILITY, range of motion, and balance. Omega-3 fatty acids and folic acid may block steps in the inflammatory response that reduce its intensity. Stress management methods such as MEDITATION help people to cope with the challenges of a chronic health condition.

Mild rheumatoid arthritis symptoms, especially pain, often respond to NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS). Acetaminophen may also relieve pain, though it does not reduce inflammation. Topical preparations such as capsaicin and complementary therapies such as ACUPUNCTURE and REIKI may provide relief from pain and other symptoms. Medications for moderate to severe symptoms may include CORTICOSTEROID MEDICATIONS, which suppress the inflammatory response, and DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (DMARDS), which block the immune response in various ways, depending on the med-

ication. Combinations of medications often provide the greatest relief. Surgery to replace seriously damaged joints with prosthetic joints becomes a treatment option when other therapeutic approaches cannot contain symptoms.

MEDICATIONS TO TREAT RHEUMATOID ARTHRITIS

acetaminophen	adalimumab
anakinra	aspirin
azathioprine	cyclosporine
etanercept	gold salts
hydroxychloroquine	ibuprofen
infliximab	ketoprofen
leflunomide	methotrexate
methylprednisolone	naproxen
prednisolone	prednisone
sulfasalazine	

Risk Factors and Preventive Measures

Researchers believe rheumatoid arthritis develops when various genetic, environmental, and hormonal factors converge. But specific risk factors remain elusive. There are no known measures to prevent rheumatoid arthritis from developing. Early diagnosis and treatment of juvenile rheumatoid arthritis are important to maintain optimal joint structure, integrity, and function. Prevention efforts focus on minimizing the consequences that the inflammation of rheumatoid arthritis causes, to preserve joint function as well as QUALITY OF LIFE.

See also AUTOIMMUNE DISORDERS; CHONDROITIN; GLUCOSAMINE; JOINT REPLACEMENT; LIVING WITH IMMUNE DISORDERS; RHEUMATIC HEART DISEASE; SAME; SCAR; STRESS AND STRESS MANAGEMENT; VASCULITIS; X-RAY.

sarcoidosis An inflammatory disorder in which multiple granulomas (nodules of hardened LYMPH and fibrous tissues) form in organs and tissues throughout the body. Sarcoidosis most commonly affects the LUNGS, LIVER, lymph nodes, eyes, and SKIN, though can affect any body structure. The granulomas typically have alternating growth and REMISSION stages, though generally cause permanent scarring. Though most people who have sarcoidosis develop small granulomas and have mild symptoms, sarcoidosis can be severe when the granulomas clump together to form large enough lesions to interfere with an organ's functions. Sarcoidosis that affects the HEART can cause life-threatening ARRHYTHMIA with high risk for SUDDEN CARDIAC DEATH.

Symptoms and Diagnostic Path

Most often sarcoidosis begins in the lungs, causing pulmonary symptoms, and in the lymph nodes. Symptoms are specific for the organ system involved. Generalized symptoms may include

- fatigue, weakness, and malaise (general sense of not feeling well)
- weight loss and loss of APPETITE
- FEVER
- night sweats and sleep disturbances
- SPLENOMEGALY (enlarged SPLEEN)
- HEPATOMEGALY (enlarged liver)
- enlarged, tender lymph nodes
- HEADACHE
- ERYTHEMA NODOSUM (red, painful skin lesions most commonly appearing on the shins)

The diagnostic path begins with BLOOD tests, chest X-RAY, and pulmonary function tests (95 percent of people who have sarcoidosis have lung involvement). The doctor may conduct other diagnostic procedures, depending on the symptoms and the necessity to rule out other causes for them. Though various procedures can show characteristic evidence of sarcoidosis, there are no conclusive diagnostic tests for sarcoidosis. Imaging procedures such as COMPUTED TOMOGRAPHY (CT) SCAN and MAGNETIC RESONANCE IMAGING (MRI) can reveal the extent of damage present as a consequence of the granulomas.

Treatment Options and Outlook

Long-term treatment (up to a year) with CORTICOSTEROID MEDICATIONS reduces the INFLAMMATION that causes symptoms and mitigates the consequential damage. Topical medications can improve skin symptoms. Severe or resistant symptoms may require IMMUNOSUPPRESSIVE THERAPY or IMMUNOTHERAPY. Even with treatment, sarcoidosis remains a chronic condition with alternating periods of remission (no symptoms) and exacerbation (resumed or intensified symptoms).

MEDICATIONS TO TREAT SARCOIDOSIS

azathioprine	cyclophosphamide
etanercept	hydroxychloroquine
infliximab	methotrexate
pentoxifylline	prednisone
tetracycline	thalidomide

Risk Factors and Preventive Measures

There are no clear risk factors for sarcoidosis, though it is more common and often more severe in African American women. Nor are there any known measures to prevent sarcoidosis from developing. Researchers believe many people have undetected sarcoidosis, making this inflammatory

disorder far more common than doctors have long believed. Early diagnosis and treatment can minimize the consequences of the inflammation and fibrosis and allow improved QUALITY OF LIFE.

See also AUTOIMMUNE DISORDERS; EYE; GRANULOMA; IMMUNE DISORDERS; LIVING WITH IMMUNE DISORDERS; LYMPH NODE; OFF-LABEL USE; SCAR.

seasonal allergies See ALLERGIC RHINITIS.

severe combined immunodeficiency (SCID) A rare, genetic immune disorder in which an infant is born with severely deficient immune capability due to the absence of leukocytes. Because the infant receives PASSIVE IMMUNITY from his or her mother at birth (and through BREASTFEEDING), the deficiency often is not apparent until age three to six months or when the infant begins to receive routine immunizations. Doctors may suspect SCID if there are other family members who have IMMUNODEFICIENCY disorders. Most often the infant's immune status becomes suspect when there are recurrent or severe infections that a healthy IMMUNE RESPONSE would accommodate. Some babies develop deep abscesses, such as in the LIVER. Others have chronic OTITIS media (middle EAR INFECTION) or SINUSITIS (sinus infection).

Early diagnosis and treatment are essential. When doctors suspect and test for SCID within the infant's first three months of life, a BONE MARROW TRANSPLANTATION can provide the ability to produce lymphocytes, essentially curing the immunodeficiency. Most often, however, parents and doctors do not suspect an immune problem until the child is six months to a year old. By that time other features of the IMMUNE SYSTEM have developed enough to reject a BONE MARROW transplant unless IMMUNOABLATION first destroys the child's own bone marrow.

Bone marrow transplantation after age six months requires extended IMMUNOSUPPRESSIVE THERAPY to allow the new BLOOD STEM CELLS to take root and become self cells within the body. The child may also need ANTIBIOTIC PROPHYLAXIS and GAMMAGLOBULIN injections to bolster the immune response until the transplant fully takes hold. Without treatment SCID is fatal by two years of age and often in the first year of life. With bone marrow transplantation the child has a good chance for normal development and a relatively healthy life.

See also ABSCESS; COMMON VARIABLE IMMUNE DEFICIENCY (CVID); GENETIC DISORDERS; INHERITANCE PATTERN; LEUKOCYTE; LIVING WITH IMMUNE DISORDERS; LYMPHOCYTE; PARTIAL COMBINED IMMUNODEFICIENCY (PCID).

Sjögren's syndrome An autoimmune disorder that affects the glands that provide moisture for the mucous membranes, notably the lacrimal (tear) glands and the SALIVARY GLANDS. Sjögren's syndrome exists in one of three forms:

- primary, in which the only structures it affects are the exocrine glands and the main symptom is dryness
- secondary, in which Sjögren's syndrome appears in conjunction with another autoimmune disorder, typically RHEUMATOID ARTHRITIS, scleroderma, or SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)
- ocular, in which symptoms affect only the eyes (lacrimal glands)

Symptoms and Diagnostic Path

Symptoms depend to some extent on the affected glands, which nearly always include the salivary glands and the lacrimal glands. The lack of moisture to the eyes can cause corneal ABRASIONS and PHOTOSENSITIVITY. However, symptoms may involve glands in mucous tissues throughout the body. Dryness affecting other mucous membranes may result in

- frequent nosebleeds (INFLAMMATION of the nasal passages)
- PERICARDITIS (inflammation of the membrane sac surrounding the HEART)
- BRONCHITIS (inflammation of the airways in the LUNGS)
- VAGINITIS (inflammation of the VAGINA)

There are no specific tests to diagnose Sjögren's syndrome. A Schirmer's test determines the moisture content of the eyes; salivary gland biopsy can reveal fibrosis and granulation typical of the inflammatory process. Doctors generally consider

the diagnosis conclusive when a person has three consecutive months of symptoms that include

- extremely dry MOUTH and swollen salivary glands
- dry, irritated membranes around the eyes and crusty accumulations on the eyelids
- inflammation of the joints

Treatment Options and Outlook

Treatment focuses on restoring moisture to the affected tissues. These efforts may include artificial tears EYE drops, moisturizing mouth rinses, vaginal moisturizing creams, and saline nasal sprays for the NOSE. Dental hygiene is crucial because the lack of saliva fosters the growth of BACTERIA and consequential DENTAL CARIES (cavities). Drinking water helps maintain moisture throughout the body. At present Sjögren's syndrome remains a chronic disorder for which there is no cure.

Risk Factors and Preventive Measures

Sjögren's syndrome affects predominantly women, with onset between the ages of 40 and 55. However, there are no known measures for preventing its development. Preventive measures instead focus on minimizing damage to the involved organ systems.

See also AUTOIMMUNE DISORDERS; CORNEA; DRY EYE SYNDROME; EPISTAXIS; LIVING WITH IMMUNE DISORDERS.

skin-associated lymphoid tissue (SALT) A loose organization of LYMPH cells and tissues that incorporates with the epidermis, the SKIN's living layer. The skin, as the body's primary interface with the external environment, is the foremost barrier to INFECTION. SALT, also called the skin IMMUNE SYSTEM (SIS), is very active. It contains large populations of mast cells, lymphocytes, and macrophages called Langerhans's cells. Its role is to intercept pathogens and other substances that manage to penetrate the physical barrier of the skin. These encounters are the basis for many of the antibodies the IMMUNE RESPONSE forms, particularly those related to allergies (HYPERSENSITIVITY REACTION).

Hypersensitivity reactions often involve dermatologic symptoms such as RASH and URTICARIA (hives). Numerous dermatologic conditions are IMMUNE DISORDERS or AUTOIMMUNE DISORDERS. Infections such as HIV/AIDS and HUMAN PAPILLOMAVIRUS (HPV) that deplete the systemic immune system result in reduced numbers of immune cells in SALT, increasing the skin's vulnerability to infection.

For further discussion of SALT within the context of the structures and functions of the immune system, please see the overview section "The Immune System and Allergies."

See also ANTIBODY; ANTIGEN; B-CELL LYMPHOCYTE; BRONCHUS-ASSOCIATED LYMPHOID TISSUE (BALT); INFECTION; KAPOSI'S SARCOMA; LYMPHOCYTE; MACROPHAGE; MAST CELL; MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT); NOSE-ASSOCIATED LYMPHOID TISSUE (NALT); OPPORTUNISTIC INFECTIONS; PATHOGEN; PHAGOCYTE; T-CELL LYMPHOCYTE; VASCULAR-ASSOCIATED LYMPHOID TISSUE (VALT); VIRUS.

systemic lupus erythematosus (SLE) A chronic autoimmune disorder in which the IMMUNE RESPONSE creates antibodies that attack the cells of various organs. SLE is a type III HYPERSENSITIVITY REACTION (immune complex reaction) that most commonly develops between the ages of 15 and 40. Nine times as many women than men have SLE, and SLE is three times more common in African American women than women of other ethnicities.

Symptoms and Diagnostic Path

The symptoms of SLE vary widely in nature and severity and are often transient (come and go). Symptoms also vary depending on the affected organ systems, making it difficult to view them collectively as indications of a single disorder. The main symptoms of SLE may include

- characteristic "butterfly" RASH across the NOSE and onto the cheeks
- fatigue, often extreme
- painful and inflamed joints
- FEVER
- enlarged lymph nodes
- loss of HAIR
- CHEST PAIN, particularly with deep BREATHING or exertion
- sensitivity to sunlight

The diagnostic path is one of exclusion. It can take months to years for doctors to rule out other causes of the symptoms and settle on the suspicion of SLE. BLOOD tests that detect antinuclear antibodies (ANAs) suggest SLE. Many people who have SLE also have other antibodies, including anti-Ro and anti-La. However, not all do, and some people have these antibodies and do not have SLE. Some people who have SLE have decreased complement factors, though other conditions can cause the same finding.

Treatment Options and Outlook

Treatment incorporates various medications, singly or in combination, that target symptoms. The most commonly used medications are NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS), antimalarial medications, CORTICOSTEROID MEDICATIONS, and IMMUNOSUPPRESSIVE MEDICATIONS. SLE is a chronic condition that medications can regulate to permit a relatively normal lifestyle. Stress exacerbates symptoms and precipitates flareups. Most people learn to identify when a flareup of symptoms is pending and to take appropriate interventions (medications and relaxation techniques) to mitigate their effects.

MEDICATIONS TO TREAT SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

cyclophosphamide	dexamethasone
hydrocortisone	hydroxychloroquine
ibuprofen	methotrexate
mycophenolate mofetil	naproxen
prednisone	

Risk Factors and Preventive Measures

The main risk factors for SLE are being female and being African American. Researchers do not know why gender and ethnicity influence the development of SLE. Preventive measures focus on reducing the complications of symptoms through prompt medical intervention and lifestyle practices, such as nutritious EATING HABITS and daily physical activity, that support health.

See also ANTIBODY; AUTOIMMUNE DISORDERS; DISCOID LUPUS ERYTHEMATOSUS (DLE); LIVING WITH IMMUNE DISORDERS; LYMPH NODE; MIND–BODY CONNECTION.

T-cell lymphocyte The type of white BLOOD cell (LEUKOCYTE) responsible for CELL-MEDIATED IMMUNITY. T-cell lymphocytes come to maturity in the THYMUS during childhood, which is why they are called T-cells. During the maturation process, T-cell lymphocytes "learn" how to recognize self and nonself antigens so they can distinguish between cells that belong to the body and cells that are foreign. Such a safeguard is necessary to keep T-cell lymphocytes from attacking the body's own cells. The thymus destroys lymphocytes that do not learn this distinction. After the thymus releases mature T-cell lymphocytes into the blood circulation, they differentiate into several subtypes. These include

- cytotoxic T-cell lymphocytes, also called killer T-cells or CD8 cells, which respond to nonself antigens to kill the cells that bear them
- helper T-cells, also called CD4 cells, which release CYTOKINES that stimulate B-CELL LYMPHOCYTE and cytotoxic T-cell lymphocyte activity
- memory T-cells, which carry specific antibodies and circulate in the blood for rapid activation should the same ANTIGEN reappear
- suppressor T-cells, which call off the IMMUNE RESPONSE when the threat to the body ends

The SPLEEN, the lymph nodes, and the MUCOSA-ASSOCIATED LYMPHATIC TISSUE (MALT) throughout the body contain millions of T-cell lymphocytes. T-cell lymphocytes also circulate in the blood and the LYMPH. T-cell lymphocytes may also be the source of disease, such as in HIV/AIDS (the VIRUS attaches to CD4 helper T-cells) and cutaneous T-cell lymphoma (CTCL), a form of cancer.

For further discussion of T-cell lymphocytes within the context of the structures and functions of the immune system, please see the overview section "The Immune System and Allergies."

See also ANTIBODY; ANTIBODY-MEDIATED IMMUNITY; CLUSTERS OF DIFFERENTIATION; LYMPH NODE; MAJOR HISTOCOMPATIBILITY COMPLEX (MHC); NATURAL KILLER (NK) CELL.

transforming growth factors (TGFs) CYTOKINES in the BLOOD circulation that attach to the surfaces

of cell membranes. Transforming growth factor alpha (TGF-alpha) stimulates the cells to grow, divide, and differentiate (cell proliferation). Lymphocytes and macrophages produce TGF-alpha. TGF-beta stimulates interleukin 1 (IL-1) production and blocks the response of lymphocytes in the inflammatory process. Lymphocytes, macrophages, and platelets secrete TGFs.

See also INFLAMMATION; INTERFERONS; INTERLEUKINS; LYMPHOCYTE; MACROPHAGE; PLATELET; TUMOR NECROSIS FACTORS (TNFS).

tumor necrosis factors (TNFs) CYTOKINES that kill tumor cells and participate in the inflammatory response. Leukocytes (white BLOOD cells) produce TNFs under stimulation from INTERLEUKINS. Tumor necrosis factor alpha (TNF-alpha), also called cachexin or cachectin, is the most active in these processes. Recombinant TNF-alpha is a treatment option for certain types of cancer. The spice turmeric (active ingredient curcumin) and the catechins in GREEN TEA also boost TNF-alpha. Overactive TNF production contributes to inflammatory AUTOIMMUNE DISORDERS such as RHEUMATOID ARTHRITIS and INFLAMMATORY BOWEL DISEASE (IBD). Doctors sometimes use therapeutic MONOCLONAL ANTIBODIES (MABS), such as infliximab and etanercept, to block TNF-alpha.

See also INFLAMMATION; LEUKOCYTE; RECOMBINANT DNA.

V

vaccine A substance that initiates an IMMUNE RESPONSE to produce antibodies that prevent INFECTION by the particular PATHOGEN. Vaccines contain attenuated live (weakened) or killed pathogens such as viruses or BACTERIA. The antigens of these pathogens activate the body's immune response, stimulating B-cell lymphocytes to produce antibodies specific to them. Genetic engineering makes it possible to produce large quantities of many vaccines in relatively short order. There are four types of vaccines:

- Attenuated vaccines contain live but weakened viruses to produce the strongest immune response. Laboratory manipulation of the VIRUS can establish narrow parameters of survival for the virus the vaccine carrier, such as temperature or acidity. These manipulations reduce the risk that the vaccine could cause infection, though such a risk exists. Often an attenuated vaccine requires only a single DOSE to establish full and long-term IMMUNITY.
- Inactivated vaccines contain killed bacteria or viruses. These pathogens still carry the antigens that will stimulate the immune response to produce antibodies but are incapable of causing infection. Though safer than attenuated vaccines, inactivated vaccines often require multiple doses or provide limited immunity.
- Acellular vaccines, also called subunit vaccines, contain particles of the virus or bacteria. These particles carry enough ANTIGEN to stimulate an immune response but are not complete enough to cause infection.
- Toxoid vaccines generate antibodies for the toxins certain bacteria generate when they cause infection. Tetanus and DIPHTHERIA are illnesses due to such toxins and the vaccines for them provide antibodies for the toxins rather than the bacteria that cause the illness.

Vaccines prevent many infectious diseases that were once major killers. Vaccination has essentially eliminated SMALLPOX worldwide, for example, and is close to eliminating POLIOMYELITIS. Some vaccines, such as for tetanus and pertussis, require multiple doses or periodic booster doses to establish full immunity. Because vaccines are effective for only the specific pathogens they contain, rapidly mutating pathogens such as the INFLUENZA virus require a new vaccine for each strain.

VACCINES

ANTHRAX	CHICKENPOX/shingles (varicella zoster viruses)
CHOLERA	diptheria, tetanus, acellular PERTUSSIS (DtaP)
DIPHTHERIA	HEPATITIS A (HAV)
Haemophilus influenzae type b (Hib)	INFLUENZA
hepatitis B (HBV)	MEASLES
LYME DISEASE	measles, MUMPS, RUBELLA (MMR)
meningococcal vaccine	pertussis
monkeypox	pneumococcal vaccine
mumps	RABIES
plague	rubella
POLIOMYELITIS	tetanus
rotavirus	typhoid
rubeola	
TUBERCULOSIS	
yellow FEVER	

Vaccines may not be effective in establishing immunity in people who are IMMUNOCOMPROMISED. Some people have allergies to the ingredients of the vaccine. Vaccines that contain attenuated live viruses sometimes use the preservative thimerosal,

which contains mercury. Because this heavy metal can cause neurologic damage, the United States has initiated a cooperative effort among vaccine manufacturers to develop thimerosal-free vaccines. Most recommended vaccines are now available without thimerosal or with minimal amounts of thimerosal.

People who travel should receive vaccines appropriate for the regions they intend to visit. The US Centers for Disease Control and Prevention (CDC) maintains a schedule of recommended travelers' immunizations at its Web site (http://www.cdc.gov).

See also ANTIBODY; ANTITOXIN; ANTIVENIN; B-CELL LYMPHOCYTE; CHILDHOOD DISEASES; INFLUENZA PREVENTION; LYMPHOCYTE; PREVENTIVE HEALTH CARE AND IMMUNIZATIONS.

vascular-associated lymphoid tissue (VALT) Loosely collected clusters of LYMPH tissue throughout the inner, mucosal layer of the walls of the BLOOD vessels. Researchers discovered VALT in the late 1990s and remain unsure of its role and functions. There do appear to be correlations between LYMPHOCYTE activity in VALT and cardiovascular conditions such as ATHEROSCLEROSIS, which many cardiologists now believe results from an inflammatory process rather than creates INFLAMMATION. Researchers do not know, however, whether VALT attempts to fight the inflammation or contributes to it. Researchers are also investigating the relationship between VALT and dissecting aortic ANEURYSM, a life-threatening condition in which the layers of the walls of the abdominal AORTA begin to separate. The separations weaken the wall of this major ARTERY, creating substantial risk for the arterial wall to rupture.

For further discussion of VALT within the context of the structures and functions of the immune system, please see the overview section "The Immune System and Allergies."

See also BRONCHIAL-ASSOCIATED LYMPHOID TISSUE (BALT); GUT-ASSOCIATED LYMPHOID TISSUE (GALT); MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT); NOSE-ASSOCIATED LYMPHOID TISSUE (NALT); SKIN-ASSOCIATED LYMPHOID TISSUE (SALT); VASCULITIS.

vasculitis A group of AUTOIMMUNE DISORDERS in which the epithelium (lining) of the BLOOD vessels becomes inflamed. The INFLAMMATION causes localized PAIN and swelling. There are numerous forms of vasculitis. They share common characteristics

TYPES OF VASCULITIS

Type of Vasculitis	Unique Symptoms	Treatment and Outlook
allergic granulomatosis and angiitis (Churg-Strauss syndrome)	primarily occurs in adults who have atopic bronchial ASTHMA affects BLOOD vessels of the LUNGS and musculoskeletal system eosinophilia (excessive number of eosinophils) and eosinophilic PNEUMONIA	CORTICOSTEROID MEDICATIONS sometimes resolves spontaneously though often is chronic course of disease may be progressive untreated eosinophilic pneumonia is life threatening
Behçet's syndrome	primarily occurs in adults who are in their 30s and is more common in men affects small arteries and veins serving epithelial tissue (SKIN and mucous membranes) and the eyes recurrent, painful ulcers in the MOUTH and VULVA that occur in clusters vision disturbances and UVEITIS inflammatory response with minor trauma such as scratches skin rashes	topical corticosteroid medications for mild skin symptoms colchicine, NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS), dapsone, or thalidomide to control ulcerations IMMUNOSUPPRESSIVE MEDICATIONS for severe symptoms that do not respond to other treatments tends to be chronic with extended periods of REMISSION (several years) PHYSICAL THERAPY and physical exercise as tolerated to maintain joint FLEXIBILITY and range of motion

and symptoms though each of which has unique traits. Vasculitis may be acute (come on suddenly, run its course, and be over) or chronic (symptoms persist or come and go). Though vasculitis can affect any kind of blood vessel in the body, it most often involves arteries.

Symptoms and Diagnostic Path

Each type of vasculitis has unique symptoms. All types of vasculitis have in common these general symptoms:

- weight loss and loss of APPETITE

Type of Vasculitis	Unique Symptoms	Treatment and Outlook
giant cell arteritis (temporal arteritis)	primarily occurs in adults over age 50 affects arteries in the upper body, notably the neck and head (carotid network) severe HEADACHE, jaw PAIN, and scalp tenderness blind spots (scotoma), blurred vision, and other vision disturbances	high-DOSE corticosteroid medications for two to four weeks long-term corticosteroid therapy delayed treatment establishes high risk for blindness resulting from optic NEUROPATHY tends to be chronic
Henoch-Schönlein purpura	primarily occurs in children under age 6 purplish RASH on the legs and feet acute illness that lasts about 2 weeks affects blood vessels of the skin, joints, gastrointestinal tract, and KIDNEYS	complete recovery without treatment (self-limiting course of disease) possible complications, though uncommon, include RENAL FAILURE and GASTROINTESTINAL BLEEDING
hypersensitivity vasculitis (leukocytoclastic vasculitis)	affects small arteries in the skin, kidneys, gastrointestinal tract, lungs, and joints palpable (raised) PURPURA, commonly on the legs	corticosteroid medications or immunosuppressive medications when involvement is systemic symptoms can be recurrent
KAWASAKI'S DISEASE (mucocutaneous LYMPH NODE syndrome)	occurs primarily in children under age 5 acute onset with high FEVER lasting five days to two weeks fever does not drop with aspirin or acetaminophen inflamed and reddened eyes, reddened and chapped lips, peeling skin, and joint pain	high-dose, intravenous GAMMAGLOBULIN aspirin most children fully recover without complications risk for coronary ARTERY INFLAMMATION and aortic ANEURYSM requires lifelong monitoring for CARDIOVASCULAR DISEASE (CVD)
microscopic polyangiitis	more common in adults over age 50 affects arteries in the kidneys, skin, lungs, and that serve PERIPHERAL NERVES fever purpura and other skin rashes neuropathy and loss of NERVE function to feet and hands alveolar hemorrhage (bleeding into the tiny air sacs in the lungs)	corticosteroid medications in combination with immunosuppressive medications trimethoprim/sulfamethoxazole (antibiotic therapy)

Type of Vasculitis	Unique Symptoms	Treatment and Outlook
polyarteritis nodosa	affects arteries in the LIVER, gastrointestinal tract, kidneys purpura and skin ulceration pain in the joints and large muscles abdominal pain HYPERTENSION	aggressive, high-dose corticosteroid medications at diagnosis immunosuppressive medications for nonresponsive or severe symptoms long-term corticosteroid therapy to control chronic disease antihypertensive therapy untreated or severe disease has high risk for death complications include renal failure, LIVER FAILURE, and HEART FAILURE
polymyalgia rheumatica	primarily occurs in adults over age 60 severe pain and inflammation in the large joints (knees, hips, shoulders)	NSAIDs corticosteroid medications chronic symptoms requiring long-term treatment may indicate underlying giant cell arteritis
Takayasu arteritis	affects the AORTA and other large arteries most common in women between ages 20 and 35 pain and weakness in the back and arm on the affected side lower BLOOD PRESSURE in the arm on the affected side headache, dizziness, and vision disturbances hypertension	corticosteroid medications immunosuppressive medications for severe symptoms ANTICOAGULATION THERAPY such as aspirin or warfarin spontaneous resolution in about 95 percent of people possible complications include STROKE, HEART ATTACK, severe hypertension, aortic aneurysm, and heart failure
thromboangiitis obliterans (Buerger's disease)	most common in men aged 20 to 40 who smoke affects blood vessels in arms, hands, legs, and feet leg cramps with walking (INTERMITTENT CLAUDICATION) altered sensation or loss of sensation in feet (paresthesia) ulcerations on fingers and toes with rapid progression to GANGRENE (tissue death)	SMOKING CESSATION rest until inflammation subsides regular walking to improve circulation and muscular support for blood vessels aggressive treatment for ulcers that develop AMPUTATION of gangrenous digits or extremities chronic condition that requires diligent lifestyle management to minimize symptoms
Wegener's granulomatosis	more common in men over age 40 affects blood vessels in the NOSE, SINUSES, THROAT, lungs, and kidneys, often causing ulcerations chronic PNEUMONITIS chronic GLOMERULONEPHRITIS forms multiple granulomas	immunosuppressive medications corticosteroid medications with mild symptoms and early diagnosis trimethoprim/sulfamethoxazole (antibiotic therapy) treatment eliminates symptoms in 50 percent of people severe or untreated symptoms can be fatal outlook best with early diagnosis and treatment

- fatigue
- FEVER
- MUSCLE aches and PAIN
- JOINT pain and swelling

The doctor may conduct BLOOD tests to measure ANTIBODY types and levels, blood cell counts, and sedimentation rate and C-REACTIVE PROTEIN level (the latter two are indicators of inflammation in the body). Diagnostic imaging procedures such as Doppler ULTRASOUND, MAGNETIC RESONANCE IMAGING (MRI) COMPUTED TOMOGRAPHY (CT) SCAN, and angiogram can demonstrate any damage to or obstruction (blockage) of the arteries and veins. Sometimes a biopsy of the involved blood vessel is necessary to confirm the diagnosis.

Treatment Options and Outlook

Some types of vasculitis are self-limiting and do not require treatment. For most, treatment may include NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS), CORTICOSTEROID MEDICATIONS, and IMMUNOSUPPRESSIVE MEDICATIONS that have cytotoxic (cell-killing) effects (such as azathioprine and cyclophosphamide). The person may take one kind of medication or a combination of medications, depending on the symptoms and their severity. Nutritional EATING HABITS and daily physical exercise such as walking also aid HEALING and improved function.

Risk Factors and Preventive Measures

Doctors do not know what causes most vasculitis, though people who have autoimmune disorders are more likely to develop some type of vasculitis. Because some forms of vasculitis have potentially severe or life-threatening complications, early diagnosis and treatment are essential for optimal recovery or disease management. Many of the medications doctors prescribe to treat vasculitis have significant side effects such as OSTEOPOROSIS so it is important to be vigilant about such conditions.

See also ARTERY; ATHEROSCLEROSIS; HYPERSENSITIVITY REACTION; LIVING WITH IMMUNE DISORDERS; OPPORTUNISTIC INFECTION; RHEUMATOID ARTHRITIS; SYSTEMIC LUPUS ERYTHEMATOSUS (SLE); VEIN.

INFECTIOUS DISEASES

Infectious diseases are illnesses that result from INFECTION *with microorganisms, also called microbes. Doctors who treat people who have infectious diseases are internists (who treat adults) or pediatricians (who treat children) who subspecialize in infectious diseases.*

This section, "Infectious Diseases," presents an overview discussion of illness due to infection and entries about systemic infectious diseases (illnesses that affect the body as a whole), their treatments, and preventive measures. Other sections in *The Facts On File Encyclopedia of Health and Medicine* discuss infections specific to individual body systems.

Health, Infection, and Disease

An infection occurs when microbes—bacteria, fungi, parasites, viruses—and other pathogens (infectious agents) such as prions invade the body. The infection causes illness (becomes a disease) when it alters in some deleterious fashion the functions of the body. Some infectious diseases are primarily a health concern only to the people who have them, such as NECROTIZING FASCIITIS, TOXIC SHOCK SYNDROME, and CANDIDIASIS. These illnesses are noncommunicable; they do not spread to other people.

sIn some situations infections affect people who have no contact with one another but somehow share a generalized source of contamination. These infections, such as occur with WATERBORNE ILLNESSES in which drinking water or recreational water contains pathogens that people consume, or in LEGIONNAIRES' DISEASE, in which building heating and air-conditioning systems disperse *Legionella pneumophilia* bacteria to all who breathe the building's air, are communicable. Though contact among infected individuals may spread the infection, the typical mode of transmission is contact with the common source.

Numerous infections spread from one person to another, directly such as through touching or sharing bodily fluids or indirectly through sneezing or coughing. These illnesses are not only communicable but also contagious: they spread easily, rapidly, and often extensively. MEASLES, for example, is one of the most highly contagious communicable diseases; 90 percent of people exposed to the virus become ill with the disease. COLDS, infectious mononucleosis (EPSTEIN-BARR VIRUS infection), and INFLUENZA are among the most common contagious diseases in the United States.

Epidemics occur when large numbers of people become ill with a communicable or contagious disease. Throughout history these waves of infection decimated families, cities, countries, and even entire civilizations. Smallpox, measles, bubonic plaque, gonorrhea, syphilis, and influenza are among the infections that raged through populations. An infectious disease is endemic when it is always present at relatively the same rate of infection within a certain geographic region, environment, or population of people. Malaria is endemic in Africa, for example, and consistently sickens thousands of people.

Until the 1950s geographic boundaries confined most infectious diseases, not because pathogens (disease-causing microbes) had much regard for natural or national borders but because few people traveled very far from home. The advent of commercial air flight changed all that. By the 1970s air travel could whisk a person literally halfway around the world in less time than it

took to drive from San Francisco to Seattle. Few infectious diseases today remain localized, though the risk of infection with them varies widely. HIV/AIDS, SEVERE ACUTE RESPIRATORY SYNDROME (SARS), and INFLUENZA stand as stark evidence that microbes, too, travel the world.

CONTAGIOUS INFECTIOUS DISEASES

ANTHRAX	CHICKENPOX
CHLAMYDIA	COLDS
DIPHTHERIA	ENCEPHALITIS
GENITAL HERPES	GONORRHEA
HEMORRHAGIC FEVERS	HEPATITIS
INFLUENZA	MEASLES
MENINGITIS	MONONUCLEOSIS, INFECTIOUS
MUMPS	SCARLET FEVER
RUBELLA	STREP THROAT
SEVERE ACUTE RESPIRATORY SYNDROME (SARS)	SYPHILIS
TRICHOMONIASIS	TUBERCULOSIS
TYPHOID FEVER	

Infectious Diseases in Medical History

Infectious diseases have mystified and plagued humanity for ages. Tuberculosis, smallpox, cholera, typhoid FEVER, and the plague itself ("Black Death") were for centuries the leading causes of disability, disfigurement, and death. Mummified remains from ancient Egypt show evidence of smallpox and tuberculosis. Disfigurement resulting from smallpox was so common through the 18th century that artists routinely painted portraits that discreetly masked or simply did not portray the extensive scars the disease left on the faces of those who survived the illness. Hippocrates wrote of "phthisis"—Greek for consumption, an apt name for tuberculosis, the disease that slowly wasted away the lives of those infected. Manuscript fragments recovered from 7th century China reference measles. Ancient Greek documents record outbreaks of "pestilence" that were likely epidemics of measles, smallpox, and perhaps plague.

For centuries doctors believed infectious diseases like tuberculosis represented some sort of inborn weakness in a family because family members often had the same illness, generation after generation. Of course, doctors today know the true reason such illnesses affected entire families: infectious diseases like tuberculosis spread from person to person, and living in close contact makes it easier if not inevitable for them to spread.

The birth of vaccination and the death of a scourge In the summer of 1796, eight-year-old James Phipps became the first success story in an effort that would reach fruition nearly 200 years later. Country doctor Edward Jenner (1749–1823) made two scratches on the boy's arm with a lancet dipped in the fluid from a smallpox sore. Nothing happened. Not then, not 14 days later when the characteristic sores of smallpox should have started erupting. The scratches healed and James remained healthy.

Six weeks earlier, Jenner had performed a similar procedure using the fluid from a cowpox sore, a much milder form of illness that doctors today know develops from infection with a virus closely related to the virus that causes smallpox. Edward Jenner did not know this but had observed that milkmaids and farm hands who recovered from cowpox did not get smallpox. Young James became ill with cowpox, as Jenner expected he would, and then soon recovered—also as Jenner expected he would. Ironically, as an adult James Phipp nearly lost his life to another infectious disease endemic throughout history, tuberculosis.

In 1966 the World Health Assembly formalized a global smallpox eradication program with vaccination, Jenner's discovery, as its foundation. The first year of the program, 15 million people throughout the world contracted smallpox; nearly a third of them died. Ten years later, on October 26, 1977, Somalian Ali Mao Moallin became the last person in the world to acquire naturally occurring smallpox (he survived). In 1980, the World Health Organization officially declared smallpox eradicated worldwide and advised countries to end vaccination programs.

Today vaccination is the cornerstone of infectious disease control and preventive medicine. Vaccines confer IMMUNIZATION for numerous infectious diseases. Many countries, including the United States, routinely administer set schedules of vaccines to children, giving them lifelong immunity that protects them from infection with diseases such as POLIOMYELITIS, MUMPS, MEASLES, CHICKENPOX, RUBELLA, PERTUSSIS (whooping COUGH), and *Haemophilus influenzae* type b (Hib).

Microbes and the mechanisms of infection As early as the 16th century some scientists postulated the existence of unseen organisms as accountable for disease. The development of the microscope gave proof to the existence of such organisms; proving their connection to disease was more difficult. The first to succeed did so in a major way. German physician Robert Koch (1843–1910) isolated and cultivated *Mycobacterium tuberculosis*, the MICROBE responsible for the Western world's most pervasive and devastating disease. By the 19th century, tuberculosis infected so many people that it was more common than not. What puzzled doctors was why some people became ill and others did not.

Koch solved this mystery in 1882 when he demonstrated the ability of *M. tuberculosis* to cause tuberculosis infection. The methods of vaccination successful in preventing smallpox, anthrax, and other infectious diseases did not work with tuberculosis, however. Not until biochemist Selman Waksman (1888–1973) discovered streptomycin, a powerful antibiotic, in 1943 were doctors finally able to gain the upper hand against tuberculosis. Waksman received the Nobel Prize in Physiology or Medicine in 1952 for his work.

Through their work to understand a disease prevalent among livestock in the 19th century, foot-and-mouth disease, German researchers Friedrich Loeffler (1852–1915) and Paul Frosch (1860–1928) expanded the spectrum of pathogens. The pair postulated the existence of a particle smaller than bacteria caused the infectious disease. However, they lacked the technology to visualize such a particle. The development of the electron microscope in 1939 gave scientists the ability to see these smallest of infective agents, viruses.

Breakthrough Research and Treatment Advances Molecular medicine advances in the late 20th century gave another enormous boost to the fight against infectious diseases. In 1995 the bacterium *Haemophilus influenzae,* an insidious microbe responsible for numerous pulmonary and gastrointestinal diseases, became the first pathogen for which researchers unraveled the genetic code. The advance led to improvements in vaccines and treatments for *H. influenzae* infections as well as other bacterial diseases.

Molecular medicine also has provided tremendous breakthroughs in understanding the modus operandi of viruses such as HIV (human immunodeficiency virus), a Machiavellian retrovirus that subverts the immune system itself to perpetuate its own survival. These breakthroughs have paved the way for new antiviral medications that target specific molecular mechanisms of HIV, slowing its progress, and show promise for the development of a vaccine that can prevent HIV infection and AIDS.

As researchers gain insight into the adaptive mechanisms of pathogens such as bacteria and viruses, they are able to develop new drugs—and drugs that work in new ways—to treat the infections these pathogens cause. This is particularly important in light of the alarming rise in DRUG-resistant infections in diseases such as tuberculosis, GONORRHEA, and staphylococcal pneumonia. New viruses also threaten public health, placing renewed emphasis on vaccines and infection control measures to stop their spread. Though the control and eradication of many infectious diseases represent many of medicine's greatest triumphs, many of medicine's greatest challenges remain these same factors.

A

abscess A localized INFECTION containing pus, a fluid-based collection of white BLOOD cells, BACTERIA, and the debris resulting from the IMMUNE SYSTEM's efforts to fight the infection. Though an abscess may cause severe PAIN and compromise the function of organs in which it occurs, an abscess represents the success of the immune system to contain and enclose the infection. An abscess can develop anywhere in the body. Symptoms vary with the abscess's location though typically include pain and swelling in the area of the infection. There often is FEVER as well. An abscess on the SKIN or near the surface of the skin may form a red nodule or an open sore. Treatment is ANTIBIOTIC MEDICATIONS when the infection is bacterial. A deep, internal abscess may require surgery to drain the pus so HEALING can take place.

See also BARTHOLIN'S CYST; FURUNCLE; HEPATIC ABSCESS; LUNG ABSCESS; PERITONSILLAR ABSCESS.

adenovirus A VIRUS family that causes INFECTION of mucous membrane tissues throughout the body. Adenoviruses are responsible for a wide range of illness including upper respiratory infection, viral CONJUNCTIVITIS, GASTROENTERITIS, and URINARY TRACT INFECTION (UTI). These infections primarily affect children age 10 and younger. Infection with one adenovirus confers immunity to that strain of virus; vulnerability to infection with other strains of adenovirus remains. Adenoviruses are highly contagious and are particularly adept at mutating and adapting. They primarily spread through

- person-to-person direct contact, such as touching
- indirect contact, such as by touching doorknobs or furniture a person infected with the virus has touched, leaving viral particles behind, or by handling tissues an infected person uses
- airborne particles, such as enter the air via sneezing and coughing
- fecal contamination, such as through changing diapers or lack of HAND WASHING after using the bathroom

The INCUBATION PERIOD (time from exposure to onset of symptoms) is usually less than 10 days and often only 2 or 3 days. Adenoviral infection seldom causes serious illness and is self-limiting (goes away on its own after running its course). Symptoms depend on the location of the infection. The doctor may take mucus samples to test for the presence of BACTERIA, as the symptoms of bacterial and viral infections are often similar. Bacterial infection requires antibiotic therapy; ANTIBIOTIC MEDICATIONS are not effective against viral infections. Treatment for adenoviral infection targets symptom relief. Because adenoviruses are so pervasive, preventing infection is nearly impossible. The most important step to minimize the risk for infection is frequent hand washing with soap and warm water. People who are IMMUNOCOMPROMISED should avoid indoor crowds to the extent possible to reduce their exposure to people infected with adenoviruses.

See also COLDS; DIARRHEA; FOODBORNE ILLNESSES; SNEEZE/COUGH ETIQUETTE.

amebiasis A parasitic INFECTION of the gastrointestinal tract. The PARASITE responsible is *Entamoeba histolytica*, a single-cell organism (an ameba) that enters the body by drinking water or eating food that contains *E. histolytica* in cyst form. The cyst is a protective encasing within which the ameba

may sustain itself in a dormant stage for weeks to months outside a host (organism that provides NUTRIENTS for a parasite). Once within the SMALL INTESTINE the cyst ruptures and the ameba emerges to enter its active stage. In this active stage the ameba, called a trophozoite, travels to the COLON (large intestine) where it feeds on intestinal BACTERIA. As the population of trophozoites increases, they burrow into the intestinal mucosa (mucous lining of the colon). Substances trophozoites secrete to digest the substances they consume cause ulcerations (sores) that produce symptoms.

Symptoms and Diagnostic Path

The symptoms of amebiasis, also called amebic dysentery, begin two weeks to four months after ingesting the contaminated food or water. They include

- abdominal cramping or ABDOMINAL PAIN
- frequent bowel movements or DIARRHEA (which may be bloody)
- FEVER

The diagnostic path includes microscopic examination of stool samples to detect the presence of either cysts or trophozoites. The doctor may also conduct sigmoidoscopy to examine the colon for the characteristic ulcerations and to rule out other causes of the symptoms.

Occasionally trophozoites penetrate far enough into the intestinal mucosa to enter the BLOOD circulation, which transports them to other organs and extends the infection. The LIVER is the most common site for distant infection, where it presents as a HEPATIC ABSCESS, though the LUNGS and the BRAIN may also become involved. In locations other than the colon the trophozoites can cause abscesses, resulting in serious or life-threatening illness. Symptoms of systemic infection depend on the affected area.

Treatment Options and Outlook

Treatment for enteric or systemic infection is a combination of ANTIBIOTIC MEDICATIONS. Appropriate treatment cures the infection; inadequately treated or untreated amebiasis becomes chronic with cycles of alternating RECURRENCE and REMISSION of symptoms. Until recently doctors believed it was possible to have an *E. histolytica* infection without symptoms. However, although it is possible to have an *E. histolytica* infection with very mild symptoms, infectious disease specialists have determined a closely related and nearly identical ameba, *E. dispar*, is the cause of infection when no symptoms are present. *E. dispar* is benign and does not require treatment.

ANTIBIOTIC MEDICATIONS TO TREAT AMEBIASIS

diloxanide furoate	iodoquinol
metronidazole	paromomycin
tinidazole	

Risk Factors and Preventive Measures

Amebiasis is most common in countries where community sanitation is poor. People who travel in such countries or are immigrants to the United States from such countries, are at highest risk for amebiasis. The infection spreads through direct contact with fecal contamination, such as by eating vegetables from contaminated soil or drinking contaminated water. People who have amebiasis can spread the infection to other people. Diligent HAND WASHING and safe food preparation are effective measures for preventing the spread of amebiasis. Travelers to countries where sanitation is substandard should follow precautions that include eating only foods that are thoroughly cooked and drinking only bottled or canned beverages (without ice) or water boiled for a minimum of one minute.

See also BOWEL MOVEMENT; DRINKING WATER STANDARDS; FOODBORNE ILLNESSES; FOOD SAFETY; GASTROENTERITIS; PERSONAL HYGIENE; PROTOZOA; WATERBORNE ILLNESSES.

antibiotic medications Drugs that kill BACTERIA and certain other microorganisms. Antibiotic medications are the mainstay of treatment for bacterial INFECTION. Broad-spectrum antibiotics are capable of killing numerous types of bacteria; narrow-spectrum antibiotics kill specific types or strains of bacteria. There are seven primary classifications of antibiotic medications—aminoglycosides, cephalosporins, macrolides, quinolones (fluorquinolones), penicillins, sulfonamides, and tetracyclines—that contain over 100 different drugs.

COMMON ANTIBIOTIC MEDICATIONS

Aminoglycosides		
gentamicin	neomycin	tobramycin
Cephalosporins		
cefaclor	cefadroxil	cefepime
cefdinir	cefoperazone	cefoxitin
cefprozil	cefprozil	ceftazidime
cefuroxime	cephalexin	cephradine
loracarbef		
Macrolides		
azithromycin	clarithromycin	erythromycin
Quinolones (Fluoroquinolones)		
cinoxacin	ciprofloxacin	enoxacin
gatifloxacin	levofloxacin	lomefloxacin
moxifloxacin	nalidixic acid	norfloxacin
ofloxacin	sparfloxacin	trovafloxacin
Penicillins		
amoxicillin	amoxicillin/ clavulanate	penicillin V potassium
Sulfonamides		
cotrimoxazole	trimethoprim	trimethoprim/ sulfamethoxazole
Tetracyclines		
doxycycline	minocycline	tetracycline

How These Medications Work

Antibiotics are either bacteriocidal (kill bacteria directly) or bacteriostatic (kill bacteria by preventing them from reproducing). Some antibiotics are effective against anaerobic bacteria (bacteria that thrive in low-oxygen environments) and others against aerobic bacteria (bacteria that require normal atmospheric oxygen concentrations to survive). Just as the strains of bacteria share common traits yet have distinguishing features, the antibiotics within a particular class have similarities and differences. Doctors match bacteria and antibiotic for greatest EFFICACY. Individual variations among people also influence antibiotic effectiveness.

Therapeutic Applications

Antibiotic medications are effective for treating bacterial infections. They have no effect on viral infections or fungal infections. Laboratory analysis of fluid or tissue samples, called culture and sensitivity, is usually necessary to determine whether an infection is bacterial. The analysis involves attempting to grow the bacteria in the laboratory, then determining which antibiotics can kill the bacteria. Types of bacteria are sensitive to specific classes of antibiotics, so knowing the general classification of the bacteria is generally sufficient for the doctor to prescribe an antibiotic medication that will kill it.

Risks and Side Effects

Antibiotic medications have numerous side effects, ranging from HYPERSENSITIVITY REACTION (allergy) to LIVER or kidney damage. Allergy to penicillin is the most common DRUG allergy. Some antibiotics diminish the effectiveness of oral contraceptives (birth control pills). Most antibiotics increase the possibility for fungal (yeast) infection because they disturb the balance of NORMAL FLORA. Common consequences of this effect are antibiotic-related DIARRHEA and oral or vaginal CANDIDIASIS (yeast infection of the mouth or vagina).

ANTIBIOTIC RESISTANCE is a significant concern. Numerous strains of bacteria have adapted to become resistant to the antibiotics commonly used to treat the infections they cause. Factors that contribute to antibiotic resistance include overprescribing of antibiotics and failure to take antibiotic medications for the full course of prescribed treatment. These factors expose bacteria to antibiotics without killing them, giving the bacteria opportunity to adapt in ways that block the actions of the antibiotics in future generations of the bacterial strain. It is essential to take antibiotic medications only when necessary and for the full course of treatment.

See also ANTIBIOTIC PROPHYLAXIS; ANTIFUNGAL MEDICATIONS; ANTIVIRAL MEDICATIONS.

antifungal medications Drugs that kill fungi (yeast). Antifungal medications are available for topical or systemic treatment. Some fungal infections require both. Antifungal medications work through various mechanisms to interfere with the ability of fungi to survive or reproduce. Broad-spectrum antifungal medications are effective for treating a variety of fungal infections; narrow-

spectrum antifungals are effective in treating specific fungal infections.

Topical preparations may be lotions, creams, ointments, sprays, powders, or suppositories. Oral preparations may be tablets and liquids to swallow. Oral preparations to treat fungal infections involving the MOUTH (THRUSH) may be liquids to swish around the mouth or tablets (troche or lozenge) to allow to dissolve in the mouth. A variety of topical antifungal medications is available as over-the-counter products that do not require a doctor's prescription. These products are to treat common fungal and yeast infections such as vaginal CANDIDIASIS and athlete's foot and jock itch (TINEA INFECTIONS).

COMMON ANTIFUNGAL MEDICATIONS

ciclopirox	clioquinol
clotrimazole	fluconazole
flucytosine	griseofulvin
itraconazole	ketoconazole
miconazole	naftifine
nystatin	oxiconazole
terbinafine	tolnaftate

Topical antifungal preparations may cause irritation to the SKIN or mucous membranes, though this is uncommon. Systemic antifungal medications may interact with other medications and have possible side effects that vary with the DRUG. It is important to tell the doctor or pharmacist of all health conditions and medications taken to treat them, including OVER-THE-COUNTER (OTC) DRUGS and herbal products, to minimize the risk for ADVERSE REACTION and DRUG INTERACTION.

See also ANTIBIOTIC MEDICATIONS; ANTIVIRAL MEDICATIONS; FUNGUS; INFECTION.

antiviral medications Medications to shorten the course and lessen the severity of illness due to viral INFECTION as well as reduce viral shedding to minimize contagiousness. Some antiviral medications are able to prevent viral infection from developing after exposure to the VIRUS. Antiviral medications mark a fine line because they must destroy viruses without damaging the cells that host them. Most antiviral medications accomplish such a task by substituting inactive molecules for key enzyme molecules in the virus's efforts to replicate.

Antiviral medications are the mainstay of therapy for HIV/AIDS. Doctors also use antiviral medications to treat viral infections such as CHICKENPOX, HERPES SIMPLEX, HERPES ZOSTER (shingles), GENITAL HERPES, INFLUENZA, and chronic HEPATITIS B. Antiviral medications have numerous and sometimes serious side effects that vary with the medication. It is important for the doctor to know all medications a person takes, including OVER-THE-COUNTER (OTC) DRUGS and herbal remedies, to minimize the risk for ADVERSE REACTION and DRUG INTERACTION.

COMMON ANTIVIRAL MEDICATIONS

acyclovir	adefovir
alpha-interferon	amantadine
famciclovir	foscarnet
lamivudine	oseltamivir
penciclovir	ribavirin
rimantadine	valacyclovir
zanamivir	

See also PREVENTIVE HEALTH CARE AND IMMUNIZATION; VACCINE.

anthrax An illness resulting from INFECTION with the bacterium *Bacillus anthracis*. Anthrax is a naturally occurring infection among wild and domestic livestock (such as cows, sheep, goats, and antelope). Anthrax is rare in people in the United States, though more common in people who live, work, or travel to countries where anthrax is more common in livestock. The BACTERIA can cause infection in people who are exposed to sick animals, such as workers on farms and in slaughterhouses. Ranchers and farmers in the United States vaccinate their livestock against anthrax. An anthrax VACCINE is also available for people.

Symptoms and Diagnostic Path

Symptoms of anthrax depend on the form of illness. Anthrax in people can take three forms:

- Cutaneous anthrax, which accounts for 95 percent of human anthrax infections, results when *B. anthracis* enters an opening in the SKIN, such as a small scratch, and causes ulcerated sores on the skin. It is highly treatable with ANTIBIOTIC MEDICATIONS and nearly everyone who receives

antibiotic therapy recovers without complications.

- Inhalation anthrax results when a person breathes *B. anthracis* into the LUNGS, where the infection causes life-threatening PNEUMONIA. Inhalation anthrax requires urgent intravenous antibiotic therapy and intensive medical care. It is difficult to avoid respiratory collapse and cardiovascular shock, which are often fatal.
- Gastrointestinal anthrax results from eating meat contaminated with *B. anthracis*. It causes NAUSEA, VOMITING (often bloody), FEVER, ABDOMINAL PAIN, and profuse DIARRHEA. Many people recover, but the illness can be life threatening.

The diagnostic path includes a comprehensive history of potential exposure to livestock or livestock products and BLOOD tests to identify the presence of characteristic antibodies. The doctor may also culture body fluids to look for *B. anthracis*.

Treatment Options and Outlook

Antibiotic therapy is the mainstay of treatment for all forms of anthrax. The earlier treatment begins, the more effective it is. Untreated anthrax in any form can be serious or fatal. A person who has anthrax cannot spread the infection to others, though health-care providers follow diligent infection control protocols when treating people who have anthrax.

ANTIBIOTIC MEDICATIONS TO TREAT ANTHRAX	
ciprofloxacin	doxycycline
levofloxacin	penicillin

Risk Factors and Preventive Measures

Exposure to potentially contaminated livestock or livestock products (meat, hides, fur) is the primary risk for naturally acquired anthrax. A vaccine to prevent anthrax is available; however, current guidelines recommend its administration only to people at high risk for exposure to *B. anthracis* or after suspected exposure to *B. anthracis*. Multiple doses over 18 months, with annual boosters, are required to establish and maintain IMMUNITY.

In the late 1990s anthrax emerged as a worldwide bioterrorism threat, with concern for the possibility of widespread infection after intentional contamination of the US mail with *B. anthracis* caused two dozen Americans to become ill with anthrax, five of whom died from the inhalation form. At present public health experts recommend the vaccine in combination with antibiotic therapy to prevent illness in people exposed to *B. anthracis*.

See also ANTIBODY; FOODBORNE ILLNESSES; SMALLPOX.

B

babesiosis An illness that results from INFECTION with the parasitic protozoan *Babesia microti*. Most people who have babesiosis do not have symptoms; the infection causes illness primarily in people who are IMMUNOCOMPROMISED or who have had SPLENECTOMY (surgical removal of the SPLEEN). The bite of the *Ixodes* tick, found in the northeastern United States, is the mode of transmission. Babesiosis is rare in other parts of the United States.

B. microti infects the erythrocytes (red BLOOD cells), causing alterations in their cell membranes that affect their ability to carry oxygen. Hemolytic ANEMIA is a key consequence of babesiosis. Symptoms may include FEVER, COUGH, and shortness of breath (DYSPNEA). The doctor uses blood tests to diagnose babesiosis. The tests show the damage to the erythrocytes and the presence of antibodies. Treatment with ANTIBIOTIC MEDICATIONS cures the infection. Rarely, a person may develop the life-threatening complication ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS).

ANTIBIOTIC MEDICATIONS TO TREAT BABESIOSIS

atovaquone	azithromycin
clindamycin	quinine sulfate

See also ANTIBODY; ERYTHROCYTE; GIARDIASIS; LYME DISEASE; PROTOZOA.

bacteria Single-cell microorganisms (microbes). Bacteria are the most ancient and primitive life forms known, with fossils dating back more than 3 billion years. A bacterium's structure is very simple, consisting of a rigid cell wall that supports and contains the cytoplasm, fragments of RNA, and a single strand of DNA within a nonencapsulated (unbordered) nucleus. Though bacteria are capable of independent existence, most require a symbiotic relationship with a host organism. The bacteria provide needed functions for the host in exchange for NUTRIENTS and safe haven.

Many types of bacteria exist in and on the body in just such a symbiotic partnership; these are part of the body's NORMAL FLORA. Bacteria in the gastrointestinal tract digest food, for example. *Bifidobacterium bifidum, Lactobacillus acidophilus,* and *Saccaromyces boulardii* are some of the more abundant bacterial families that reside in the small intestine. However, when normal flora bacteria are able to establish themselves in tissues other than their natural habitat or their numbers become abundant, they cause INFECTION. *Escherichia coli*, for example, are abundant normal flora in the COLON, where they work to prepare the residue of digestion for elimination from the body. *E. coli* also synthesize VITAMIN K, which is essential for COAGULATION (BLOOD clotting). When *E. coli* escape from their habitat, however, they cause infections such as VAGINITIS or URINARY TRACT INFECTION (UTI).

THE "BAD" *E. COLI*: O157:H7

The bacterial family *Escherichia coli* is extensive and ubiquitous—its many strains live in the gastrointestinal systems of nearly all animals. *E. coli* O157:H7, NORMAL FLORA in cattle, is a family member of great notoriety for the potential of severe illness it presents in people. The toxin this strain releases can destroy red BLOOD cells in such volume that the KIDNEYS fail, a condition called HEMOLYTIC UREMIC SYNDROME. *E. coli* O157:H7 enters the human food chain as a foodborne illness.

Bacteria that cause infection are pathogens. Most pathogenic bacteria exist in the natural envi-

ronment, they are harmful to human health, and the IMMUNE SYSTEM establishes mechanisms to stop, contain, or attack them should they enter the body. Bacteria can cause infection and illness by destroying the cells they invade or by releasing toxins. ANTIBIOTIC MEDICATIONS treat bacterial infections.

Traditional classification systems view bacteria according to their physical (morphologic) characteristics because these are the traits perceptible with the use of a microscope, the first tool available for viewing microbes. These characteristics provide basic information about the particular bacterial family that is important to doctors when choosing antibiotic medications to treat bacterial infections. Methods made available through advances in molecular medicine during the latter years of the 20th century, such as ribosomal analysis and DNA sequencing, allow improved understanding of how bacteria function both to support health and to cause illness.

ILLNESSES CAUSED BY BACTERIAL INFECTION

ABSCESS	ANTHRAX
APPENDICITIS	bacterial MENINGITIS
BOTULISM	CAMPYLOBACTERIOSIS
CHLAMYDIA	CHOLERA
COLD SORE	CONJUNCTIVITIS
DIPHTHERIA	EPIGLOTTITIS
FOLLICULITIS	FURUNCLE
GONORRHEA	HERPES ZOSTER
INFECTIOUS ARTHRITIS	LEGIONNAIRES' DISEASE
LISTERIOSIS	LYME DISEASE
MASTOIDITIS	NECROTIZING FASCIITIS
ORBITAL CELLULITIS	OSTEOMYELITIS
PERICARDITIS	PERITONSILLAR ABSCESS
PNEUMOCOCCAL PNEUMONIA	RHEUMATIC HEART DISEASE
ROCKY MOUNTAIN SPOTTED FEVER	SCARLET FEVER
SEPTICEMIA	STAPHYLOCOCCAL SCALDED SKIN SYNDROME
STREP THROAT	
SYPHILIS	TUBERCULOSIS
TYPHOID FEVER	

See also CELL STRUCTURE AND FUNCTION; CHILDHOOD DISEASES; *ESCHERICHIA COLI* INFECTION; NUTRITIONAL THERAPY; PATHOGEN.

botulism A potentially life-threatening illness resulting from INFECTION with the anaerobic bacterium *Clostridium botulinum*. The BACTERIA are naturally present in soil, where they encase themselves in spores. In the body, the bacteria release a toxin that blocks the release of acetylcholine, a NEUROTRANSMITTER that facilitates NERVE impulses from neurons to MUSCLE cells, causing PARALYSIS that may range in severity from mild to life-threatening. There are three types of botulism:

- Foodborne botulism results from eating improperly canned or cooked foods contaminated with *C. botulinum* spores. Because the bacteria are anaerobic, they thrive in the relatively oxygen-free environment of canned, bottled, or otherwise contained foods. Foodborne botulism most commonly causes gastrointestinal symptoms such as abdominal cramping and DIARRHEA, though can cause systemic symptoms that may include paralysis of the chest muscles.
- Wound botulism develops in traumatic injury wounds that close over after the injury, trapping bacteria within them. Usually the injury involves some sort of contact with soil. This type of botulism can result in the infection commonly called gas GANGRENE. Often treatment requires surgery to open and clean the wound, removing damaged and dead tissue, along with administration of intravenous ANTIBIOTIC MEDICATIONS.
- Infant botulism occurs in children under age one year whose gastrointestinal tracts are not fully developed. The most common source of *C. botulinum* that causes infant botulism is unpasteurized honey. In an older child or adult the NORMAL FLORA and environment of the gastrointestinal tract would neutralize the few *C. botulinum* spores honey typically contains, but the infant's system lacks the maturity to do this.

Symptoms and Diagnostic Path

Symptoms begin 2 to 10 days after exposure. Early neurologic symptoms include vision disturbances, difficulty swallowing and speaking, and drooping eyelids (PTOSIS). As the infection progresses, paralysis may develop throughout the body. In foodborne botulism symptoms also include NAUSEA, VOMITING, and diarrhea. In wound botulism, there may also be PAIN and swelling at the wound site though usually the wound appears normal.

The diagnostic path includes a comprehensive NEUROLOGIC EXAMINATION and testing for the presence of *C. botulinum* in either a stool sample or sample of the suspected food source.

Treatment Options and Outlook

Treatment in older children and adults is hospitalization and prompt administration of trivalent ABE ANTITOXIN to counter the effects of the toxin the *C. botulinum* bacteria produce. Additional treatment for wound botulism is intravenous antibiotics, usually high doses of penicillin or clindamycin. Treatment for infant botulism is the antibiotic amoxicillin. With prompt and appropriate treatment many people fully recover from botulism, though some people have weakness, paralysis, or other neurologic symptoms.

Risk Factors and Preventive Measures

C. botulinum spores are present in soil and thus can contaminate vegetables and fruits. The risk for infection occurs with improperly canned or processed foods because the *C. botulinum* bacteria thrive and vastly multiply in the anaerobic environment. It is not possible to detect their presence by the appearance, smell, or taste of the contaminated food, though often the can or jar lid bulges. Home-canned foods are more commonly the source of foodborne botulism. Infants under one year should not eat honey or foods that contain honey, as unpasteurized honey is a common source of *C. botulinum* spores that are not a health risk to adults but can cause illness in infants. Wound botulism may develop even when the person takes antibiotics because the broad-spectrum antibiotics typically prescribed are not effective against *C. botulinum*. Diligent cleansing of injuries that have soil contamination reduces the risk for wound botulism.

See also ANTIBIOTIC MEDICATIONS; BOTULINUM THERAPY; FOODBORNE ILLNESSES; FOOD SAFETY; GUILLAIN-BARRÉ SYNDROME; NEURON; WATERBORNE ILLNESSES.

C

campylobacteriosis An illness that results from INFECTION with the bacterium *Campylobacter jejuni.* The BACTERIA are commonly present in domestic birds such as chickens and turkeys without causing illness in the birds; the typical source of infection in people is undercooked poultry (especially chicken) or cross-contamination that occurs from improper handling and preparation of poultry. Health experts estimate that half the chickens slaughtered for market in the United States carry *C. jejuni,* though proper handling prevents cross-contamination and thorough cooking kills the bacteria so it does not cause infection. It is not possible to tell whether *C. jejuni* contaminates raw chicken; appropriate FOOD SAFETY measures are essential when preparing any poultry or meat. Other animal-based foods may also be the source of *C. jejuni*, nobly unpasteurized milk. Campylobacteriosis is one of the most common FOODBORNE ILLNESSES.

Symptoms and Diagnostic Path

Symptoms develop two to five days after consuming contaminated food or water and include DIARRHEA, abdominal cramping, and FEVER. Some people also have NAUSEA and VOMITING. The diarrhea may be slightly bloody. Many people do not seek medical treatment because the infection is self-limiting and generally runs its course in a few days. The doctor can positively identify *C. jejuni* as the culprit through cultures of stool samples, though this is not usually necessary.

Treatment Options and Outlook

Campylobacteriosis is self-limiting, with symptoms ending within five days. Most people who develop campylobacteriosis require only supportive treatment such as increased fluid consumption to prevent DEHYDRATION until the diarrhea runs its course. The doctor may prescribe an antibiotic medication such as erythromycin when symptoms are severe or recur. Rare complications of campylobacteriosis include GUILLAIN-BARRÉ SYNDROME, an autoimmune disorder that causes neurologic symptoms, including MUSCLE weakness and PARALYSIS. Though Guillain-Barré syndrome is rare, health experts believe campylobacteriosis triggers about 40 percent of cases.

Risk Factors and Preventive Measures

Proper food handling, thoroughly cooking chicken and other poultry, and drinking pasteurized milk are highly effective measures for preventing campylobacteriosis. Preventive food safety measures include

- wash hands with warm water and soap after handling raw poultry and meat
- use separate utensils, cutting knives, and cutting surfaces for preparing poultry and meats
- wash food preparation surfaces, knives, and utensils with hot water and soap immediately after using them

See also HAND WASHING; WATERBORNE ILLNESSES.

candidiasis An illness resulting from INFECTION with fungi (also called yeasts) from the *Candida* family, most commonly *Candida albicans,* though other *Candida* species may also cause infection. Candidiasis, commonly called yeast infection (or THRUSH when it involves the MOUTH), affects the mucous membranes of the mouth, ESOPHAGUS, urinary tract, or VAGINA. *Candida* may also affect the perineal area, such as in DIAPER RASH.

Yeasts and bacteria are NORMAL FLORA (microorganisms present in health) that keep each other in

balance. They are vital for numerous body functions such as digestion. Candidiasis develops when there is a disturbance of the balance that allows *Candida* to flourish, such as a change in the acid balance (pH) of the tissues, suppression of normal flora bacteria with antibiotic therapy, compromised immune function, and excessive moisture. Candidiasis is the most common cause of ESOPHAGITIS, VAGINITIS in women, and diaper rash in infants.

Chronic candidiasis may indicate an underlying health condition such as DIABETES and is often the first sign of HIV INFECTION. A doctor should conduct a comprehensive health examination in people who have four or more episodes of candidiasis in a year.

Symptoms and Diagnostic Path

Symptoms of candidiasis vary with the site of infection. In the mouth there are white patches on the tongue and inner cheeks (oral mucosa). Candidal vaginitis produces a characteristic "cheesy" discharge and intense itching. Candidal diaper rash appears as red, fragile blotches or sores with white pustules. In candidal esophagitis the doctor can see characteristic ulcerations on endoscopic examination. Invasive candidiasis may present with FEVER along with indications of LIVER disease such as JAUNDICE, neurologic impairment when infection involves the CENTRAL NERVOUS SYSTEM, cardiovascular compromise with candidal ENDOCARDITIS (infection of the lining of the HEART), or RENAL FAILURE when infection involves the KIDNEYS.

The diagnostic path for superficial (oral, esophageal, perineal, or genital) candidiasis includes taking samples of the white patches or discharge for examination under the microscope, which reveals the presence of abundant *Candida* colonies. BLOOD cultures show *Candida* growth in invasive candidiasis.

Treatment Options and Outlook

Superficial candidiasis is common and easily treatable with ANTIFUNGAL MEDICATIONS. HEALING occurs without residual consequences, though infection may recur when conditions are favorable. Invasive or systemic candidiasis, which occurs when the *Candida* enter the blood circulation, is a very serious infection that requires treatment with intravenous antifungal medications. Invasive candidiasis can be life-threatening in IMMUNOCOMPROMISED people.

ANTIFUNGAL MEDICATIONS TO TREAT CANDIDIASIS

amphotericin-B	clotrimazole
econazole	fluconazole
flucytosine	ketoconazole
micafungin	miconazole
nystatin	

Risk Factors and Preventive Measures

DIABETES, long-term use of CORTICOSTEROID MEDICATIONS, antibiotic therapy, and HIV/AIDS are among the key risk factors for candidiasis. A normal course of ANTIBIOTIC MEDICATIONS prescribed to treat bacterial infection may cause candidal vaginitis; women who are susceptible to vaginal candidiasis should discuss prophylactic antifungal therapy with their doctors. Preventive measures for candidal diaper rash, a consequence of both pH change (from URINE contact with the SKIN) and excessive moisture, include frequent diaper changes and application of protective cream or ointment to keep the perineal area clean and dry.

See also ENDOSCOPY; FUNGUS; OPPORTUNISTIC INFECTION; TINEA INFECTIONS.

carrier A person who has a bacterial or viral INFECTION but does not show symptoms or become ill because of the infection and yet can pass the infection on to other people. A third of people who have infectious HEPATITIS are carriers, for example. In some circumstances treating the infection eliminates it so the person cannot pass the infection to others. In other circumstances, such as hepatitis B VIRUS (HBV) infection, there is no effective treatment and the person is capable for life of transmitting the infection.

See also BACTERIA; GENETIC CARRIER; MODES OF TRANSMISSION; PARASITE.

chickenpox A common childhood illness that results from INFECTION with the varicella-zoster VIRUS, a member of the herpesvirus family. Chickenpox, also called varicella disease, is highly contagious, spreading through direct contact and

exposure to airborne droplets containing the varicella-zoster virus. The INCUBATION PERIOD (time from exposure to illness) is 10 to 21 days.

Symptoms and Diagnostic Path

The first symptoms are general and include FEVER, HEADACHE, loss of APPETITE, and sometimes NAUSEA and VOMITING. Within two days the characteristic pox emerge. These fluid-filled blisters cover the body and sometimes even occur within the MOUTH, on the surface and sometimes the inside of the eyelids, and in the VAGINA. The blisters itch intensely. In two or three days the fluid within the blisters oozes out and a crust forms, after which the itching subsides. However, new batches of blisters may continue to emerge in clusters for three to five days after the first outbreak.

Diagnosis is straightforward as the pox are characteristic and the illness is so highly contagious that it affects large numbers of people. Many health-care providers do not want to see people who are likely to have chickenpox because of the contagiousness and because treatment is supportive, not therapeutic. The person is contagious from two days before the onset of symptoms until all the pox crust over.

Treatment Options and Outlook

Most people do not require treatment other than supportive care to improve comfort. Such care may include

- calamine lotion applied to the blisters to relieve itching
- oral ANTIHISTAMINE MEDICATION to relieve itching
- acetaminophen or NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) such as ibuprofen to relieve headache, fever, and general discomfort
- tepid baths with oatmeal in the water to relieve itching

Isolation is important until all the pox have blistered. Schools may require children to remain home until the crusts are no longer apparent. Most people recover and are able to return to normal activities within 7 to10 days. The pox heal without scarring unless they become infected, which may happen with excessive scratching.

Do not give aspirin to anyone who has chickenpox, as doing so creates the risk for developing REYE'S SYNDROME. Reye's syndrome is a serious neurologic condition that can be fatal.

ANTIVIRAL MEDICATIONS can significantly lessen the severity and length of illness when taken within 24 hours of the first pox. However, doctors typically reserve antiviral medications for people at risk for severe illness—infants under one year of age, pregnant women, and people who are IMMUNOCOMPROMISED—because the normal course of illness is short and has very low risk for significant complications. The most common complication of chickenpox is bacterial infection of the pox that results from scratching, which introduces BACTERIA into the blisters. Complications that are rare though possible include ENCEPHALITIS, PNEUMONIA, and REYE'S SYNDROME.

The varicella-zoster virus remains in the body after the illness of chickenpox runs its course, retreating to the NERVE roots where it apparently enters a stage of dormancy. In 90 percent of people the virus never re-emerges; however, in about 10 percent of people the virus causes HERPES ZOSTER (shingles) years to decades after chickenpox.

Risk Factors and Preventive Measures

Exposure to the varicella-zoster virus is the only risk factor for chickenpox. It is very difficult to avoid exposure because the MODES OF TRANSMISSION are multiple. As well, the extremely contagious nature of the infection coupled with the extended incubation period means exposure often occurs before people realize they are ill; outbreaks of chickenpox are typically widespread. A VACCINE for chickenpox is part of the routine IMMUNIZATION schedule for children in the United States. The vaccine prevents chickenpox in about 85 percent of people who receive it and significantly reduces the severity and length of illness in those who acquire the infection.

See also BLISTER; CHILDHOOD DISEASES; MEASLES; MUMPS; OCULAR HERPES ZOSTER; PREVENTIVE HEALTH CARE AND IMMUNIZATION; RUBELLA; SNEEZE/COUGH ETIQUETTE.

chlamydia Illness resulting from INFECTION with the bacterium *Chlamydia trachomatis*. Chlamydia is one of the most common SEXUALLY TRANSMITTED DISEASES (STDS) in the United States, infecting an estimated three million people each year. However, fewer than a third seek treatment because their symptoms are mild or they do not have symptoms and do not know they have chlamydia. Half of men and two thirds of women who have chlamydia experience no symptoms, though they nonetheless pass the infection to their sex partners. Doctors sometimes call chlamydia the "silent STD" for this reason. A woman may also transmit chlamydia to her infant during vaginal childbirth.

Symptoms and Diagnostic Path

When symptoms are present, they generally appear within three weeks of exposure. Men may experience a discharge from the PENIS and PAIN with URINATION. Women may experience vaginal discharge and burning with urination in the early stages of infection, and later may have pelvic pain, low BACK PAIN, discomfort or pain with SEXUAL INTERCOURSE, and vaginal bleeding between periods.

The diagnostic path includes a physical examination (with PELVIC EXAMINATION for women) and laboratory testing of discharge samples to detect the presence of *C. trachomatis* bacteria. Because chlamydia often does not cause symptoms, diagnosis may occur as a consequence of ROUTINE MEDICAL EXAMINATION.

Treatment Options and Outlook

Treatment is with oral (by MOUTH) ANTIBIOTIC MEDICATIONS. It is important for sex partners to also receive treatment because when they do not, reinfection will occur. Appropriate antibiotic therapy eliminates the infection. People who receive treatment recover fully. However, scarring and other damage that occurs because of long-term infection in a woman is typically permanent, and can result in INFERTILITY.

Untreated chlamydia has significant consequences for women, about half of whom develop PELVIC INFLAMMATORY DISEASE (PID). PID is a leading cause of ECTOPIC PREGNANCY and of infertility. The infection damages and scars tissue in the FALLOPIAN TUBES, blocking the pathway by which OVA (eggs) travel from the OVARIES to the UTERUS. Scarring may also affect the uterus, preventing implantation in the earliest stages of PREGNANCY. Untreated chlamydia increases a woman's risk for HIV infection.

ANTIBIOTIC MEDICATIONS TO TREAT CHLAMYDIA

amoxicillin	azithromycin
doxycycline	erythromycin
levofloxacin	ofloxacin

Risk Factors and Preventive Measures

Nearly all chlamydia infections in adults occur as a result of vaginal, oral, or anal sex with someone who has the infection. Women in particular often are reinfected after they receive treatment but their sex partners do not. Infants may acquire chlamydia from their mothers during birth and may develop chlamydial CONJUNCTIVITIS (infection of the tissues around the eyes) or PNEUMONIA. Safer sex practices, such as monogamous relationships and condom use, are the most effective measures for preventing chlamydia. Health experts recommend annual chlamydia screening for sexually active women who are under age 25 or have multiple sex partners.

See also GENITAL HERPES; GONORRHEA; HUMAN PAPILLOMAVIRUS (HPV); REITER'S SYNDROME; SCAR; SEXUAL HEALTH; SEXUALLY TRANSMITTED DISEASE (STD) PREVENTION; SYPHILIS.

cholera An illness resulting from INFECTION with the bacterium *Vibrio cholerae*. The BACTERIA release a toxin in the SMALL INTESTINE that disrupts the electrolyte balance, drawing vast amounts of water into the small intestine and causing sudden, profuse DIARRHEA. The diarrhea in turn causes severe DEHYDRATION. The incubation period (time from exposure to illness) is a few hours to a few days.

Cholera nearly always occurs in conditions of poor sanitation and is endemic (constantly present) in many areas of the world where community sanitation is chronically substandard. Infection results from drinking water contaminated with *V. cholerae*, eating raw shellfish harvested from contaminated water, or eating uncooked foods rinsed with contaminated water.

BLOOD TYPE AND CHOLERA SUSCEPTIBILITY

For reasons researchers do not understand, people who have BLOOD TYPE O have twice the likelihood of contracting cholera than others, and people who have blood type AB seldom become infected.

Though the profuse, watery diarrhea of cholera has a characteristic appearance and smell, the doctor may perform a stool culture to confirm the diagnosis. Treatment is oral rehydration solution (ORS) to replace the massive loss of fluid that occurs with the diarrhea, which can exceed a quart an hour. Doctors may prescribe tetracycline to shorten the course of illness when symptoms are especially severe, though most people recover with appropriate rehydration.

Cholera is rare in the United States, though people who travel to parts of the world where cholera is endemic are at risk for infection. Preventive measures include frequent HAND WASHING; drinking only bottled beverages or water purified through boiling, chlorination, or iodinization; and avoiding raw foods.

See also DRINKING WATER STANDARDS; WATERBORNE ILLNESSES.

coccidioidomycosis An illness resulting from INFECTION with the spores of the fungus *Coccidioides immitis*, which occurs naturally in the soil in desert environments, inhaled into the LUNGS. Coccidioidomycosis affects the respiratory tract, primarily the lungs. About half of people infected with *C. immitis* do not become ill. The IMMUNE SYSTEM can successfully neutralize small numbers of *C. immitis* spores before they cause illness, though the person will test positive for infection. Exposure to high numbers of spores is more likely to result in illness. Among those who develop symptoms of coccidioidomycosis, commonly called valley FEVER, illness may be acute, chronic, or disseminated. In people who are IMMUNOCOMPROMISED, coccidioid omycosis may occur as an OPPORTUNISTIC INFECTION.

Symptoms and Diagnostic Path

The most common form of coccidioidomycosis is acute, in which symptoms develop within four weeks of exposure. Symptoms include

- nonproductive (dry) COUGH and CHEST PAIN
- FEVER
- fatigue
- chills and night sweats
- diminished APPETITE and weight loss
- HEADACHE
- MUSCLE and JOINT PAIN
- RASH
- LYMPHADENOPATHY (swollen LYMPH nodes)

The diagnostic path includes chest X-RAY and coccidioidin SKIN test. The skin test is positive 21 days after exposure. BLOOD tests may also show elevated antibodies.

Treatment Options and Outlook

Though the infection is self-limiting and resolves within three to six months without treatment in most people, doctors often prescribe ANTIFUNGAL MEDICATIONS to eradicate the infection more quickly and reduce the likelihood for complications, which may include MENINGITIS. Most people recover without residual effects. Some people develop chronic infection, in which symptoms recur. About 1 percent of people develop disseminated disease (also called progressive), in which the infection enters the blood circulation and travels to other structures and organs. Extended, sometimes lifelong, treatment with antifungal medications is required for chronic and disseminated coccidioidomycosis. People who are immunocompromised, take IMMUNOSUPPRESSIVE THERAPY, or are of Filipino or African American heritage have especially high risk for disseminated disease.

ANTIFUNGAL MEDICATIONS TO TREAT COCCIDIOIDOMYCOSIS

amphotericin B	fluconazole
itraconazole	ketoconazole

Risk Factors and Preventive Measures

The primary risk factor for coccidioidomycosis is exposure to soil, especially dust, containing *C. immitis* spores. Public health officials often note spikes in reported infections after desert dust storms. Farm and ranch workers, construction workers, and archaeologists have increased risk

for infection through continued exposure to soil and dust.

See also ASTHMA; BRONCHITIS; HISTOPLASMOSIS; PLEURAL EFFUSION; PNEUMONIA.

colds Common illnesses resulting from INFECTION with one of more than 200 variations of rhinovirus, a family of highly contagious viruses that infiltrate the nasal mucosa (mucous membranes that line the inside of the NOSE and the SINUSES). Because so many variations of rhinovirus can cause colds, most people get several colds a year. Children may get 8 to 10 colds in a year; adults may get half as many. Colds are the most common viral infections.

Symptoms and Diagnostic Path

The characteristic symptoms of a cold affect the nose and sinuses and represent the IMMUNE SYSTEM's efforts to rid the body of the VIRUS rather than the actions of the virus itself. Symptoms of a cold include

- runny nose (rhinitis) and sinus congestion
- sneezing
- yellowish green nasal discharge

Some people develop sore THROAT (PHARYNGITIS) and COUGH as a consequence of postnasal drip, and the sinus congestion often causes HEADACHE. Colds do not typically cause FEVER or MUSCLE aches; these and other more extensive symptoms suggest a different viral infection such as INFLUENZA (the flu). In children, EAR infections (OTITIS media) may occur as a secondary illness because the congestion clogs the eustachian tubes, causing fluid to accumulate in the middle ear.

Treatment Options and Outlook

Colds are self-limiting, generally running their course in five to seven days. Treatment is supportive, targeting relief of symptoms. Many over-the-counter (OTC) cold products contain decongestant medications, cough suppressants, ANALGESIC MEDICATIONS, and sometimes ANTIHISTAMINE MEDICATIONS. Drinking plenty of fluids is important to help loosen nasal secretions, particularly when taking decongestant medications that dry out the mucous membranes. Chicken soup, a time-honored folk remedy, may boost the immune system's efforts to fight the infective VIRUS. ANTIBIOTIC MEDICATIONS are *not* effective in treating viral infections. Doctors may prescribe ANTIVIRAL MEDICATIONS to people at risk for complications, generally those who are IMMUNOCOMPROMISED. Antiviral medications can shorten the course of the cold. Complications that may develop include BRONCHITIS and PNEUMONIA, both of which can have serious health consequences for people who lack a strong IMMUNE RESPONSE.

Risk Factors and Preventive Measures

Rhinoviruses are ever present. They tend to cause infection (colds) during times when people are together indoors for extended periods of time—winter. The rhinovirus particles travel through the air and attach themselves to surfaces such as doorknobs. The most effective measure for preventing colds is diligent HAND WASHING. Minimizing exposure to large crowds of people (such as in shopping malls, theaters, and restaurants) lowers the risk for exposure to viruses that cause colds. There is some evidence that the herbal product ECHINACEA can prevent or lessen the severity of colds. Zinc supplements boost immune function, helping the body resist infection with rhinoviruses.

See also ALLERGIC RHINITIS; EUSTACHIAN TUBE; SNEEZE/COUGH ETIQUETTE.

cryptococcosis An illness that results from INFECTION with the FUNGUS *Cryptococcus neoformans*, which is abundant in soil worldwide. Cryptococcosis may affect the MENINGES (membranes covering the BRAIN and SPINAL CORD), the LUNGS, or the SKIN. Infection is most likely in people who are IMMUNOCOMPROMISED and is a particular risk in those who have HIV/AIDS, Hodgkin's lymphoma, or SARCOIDOSIS. Though typically a mild and self-limiting illness, cryptococcosis disseminate (become widespread throughout the body).

Most people have mild, generalized symptoms of illness such as HEADACHE, muscle aches, COUGH, and chest tightness. Significant exposure to *C. neoformans* or compromised immune function causes more severe symptoms. Culture of body fluid samples provides definitive diagnosis. Mild cryptococcosis does not require treatment and most people recover without complications. Doctors prescribe

ANTIFUNGAL MEDICATIONS to treat severe symptoms or cryptococcosis in people who are immunocompromised (including those who have HIV/AIDS); long-term treatment may be necessary.

ANTIFUNGAL MEDICATIONS TO TREAT CRYPTOCOCCOSIS		
amphotericin B	fluconazole	flucytosine

See also CANDIDIASIS; COCCIDIOIDOMYCOSIS; CRYPTOSPORIDIOSIS; OPPORTUNISTIC INFECTION.

cryptosporidiosis An illness that results from INFECTION with the PARASITE *Cryptosporidium parvum,* which lives in the gastrointestinal tract of numerous animals and passes into the environment, primarily bodies of fresh water such as rivers and lakes, through the feces. The parasites form cysts that are highly resistant even to chemical disinfectants such as chlorine.

People acquire infection with *C. parvum* through drinking or unintentionally swallowing (such as when swimming) contaminated water. The parasites may also be present in foods rinsed or prepared with contaminated water. The INCUBATION PERIOD is 2 to 10 days and the illness lasts about 2 weeks. During the incubation period and when symptoms are present, the infection is contagious and the person may pass it to others. Proper HAND WASHING and other PERSONAL HYGIENE measures are essential to reduce this risk.

The primary symptom of cryptosporidiosis is profuse, watery DIARRHEA. In addition to the diarrhea, many people have abdominal cramping and low-grade FEVER. Treatment is supportive, emphasizing fluid replacement to prevent DEHYDRATION due to the diarrhea. People who are IMMUNOCOMPROMISED may require hospitalization for adequate fluid replacement and medical management of the diarrhea. Most otherwise healthy people fully recover after the infection runs its course.

See also AMEBIASIS; CYCLOSPORIASIS; DRINKING WATER STANDARDS; FOODBORNE ILLNESSES; GIARDIASIS; OPPORTUNISTIC INFECTION; WATERBORNE ILLNESSES.

cyclosporiasis An illness that results from INFECTION with the PARASITE *Cyclospora cayetanensis.* The *Cyclospora* come to maturity in warm, moist environments after excretion in the feces of people who have the infection. This parasite, unlike most, cannot cause immediate infection so people who are infected are not contagious. People acquire infection with *Cyclospora* through eating foods or drinking water contaminated with the parasites. The *Cyclospora* infect the SMALL INTESTINE, causing abdominal cramping and watery DIARRHEA. Some people also have low-grade FEVER and generalized discomfort.

The incubation period (time from infection to illness) is five to seven days. Diagnosis is through laboratory examination of stool samples, which reveals the *Cyclospora* cysts. Treatment is a course of therapy with ANTIBIOTIC MEDICATIONS, usually the combination antibiotic drug trimethoprim-sulfamethoxazole (TMP-SMZ), along with diligent rehydration. Most people recover rapidly and completely with treatment. Without treatment, relapses of symptoms are common and can continue over a period of several months before full recovery occurs.

See also COCCIDIOIDOMYCOSIS; CRYPTOCOCCOSIS; CRYPTOSPORIDIOSIS; FOODBORNE ILLNESSES; FOOD SAFETY; OPPORTUNISTIC INFECTION; WATERBORNE ILLNESSES.

cytomegalovirus (CMV) A member of the herpesvirus family, also called human herpesvirus-5 (HHV-5). Like other herpesviruses, CMV is ubiquitous throughout the world—85 percent of Americans have CMV INFECTION by age 40. However, CMV infection primarily causes illness only in people who are IMMUNOCOMPROMISED, such as people who have HIV/AIDS or who take long-term IMMUNOSUPPRESSIVE THERAPY after ORGAN TRANSPLANTATION. CMV is also a significant risk for the unborn child of a woman whose initial infection with the VIRUS occurs during PREGNANCY. CMV virus crosses the PLACENTA to the fetus, causing congenital CMV infection. Most infants are born unharmed; however, CMV infection can affect hearing, vision, and intellectual capacity.

When CMV infection causes illness, symptoms typically include NAUSEA, VOMITING, DIARRHEA, JAUNDICE, and FEVER. The person often has an enlarged and tender LIVER (HEPATOMEGALY) and SPLEEN (SPLENOMEGALY). Doctors may suspect infectious mononucleosis or HEPATITIS, though tests for these conditions come back negative. A BLOOD test can

detect the presence of CMV antibodies to confirm the diagnosis of CMV infection. Though most people recover without complications, CMV infection can be serious or fatal in people who are immunocompromised. ANTIVIRAL MEDICATIONS are not very effective in treating the infection; treatment primarily targets symptoms.

See also ANTIBODY; EPSTEIN-BARR VIRUS; HERPES SIMPLEX; HERPES ZOSTER; MONONUCLEOSIS, INFECTIOUS; OPPORTUNISTIC INFECTION.

D–E

diphtheria An illness that results from INFECTION with the bacterium *Corynebacterium diphtheriae*. Routine childhood IMMUNIZATION has made diphtheria rare in the United States, though the infection can occur in people who do not receive a booster VACCINE every 10 years and is common in other parts of the world.

Infection may involve the NOSE and THROAT (respiratory diphtheria) or the SKIN (cutaneous diphtheria). *C. diphtheriae* BACTERIA that infect the throat produce a toxin that causes a thick layer of cells and mucus to accumulate in the throat, forming a membrane that impairs BREATHING. Respiratory diphtheria is life threatening and requires urgent administration of diphtheria ANTITOXIN, which counters the toxin the *C. diphtheriae* bacteria produce, in combination with ANTIBIOTIC MEDICATIONS to kill the *C. diphtheriae* bacteria (typically erythromycin or penicillin G). Diphtheria that occurs in the United States is most often cutaneous. Cutaneous diphtheria causes painful, red sores on the skin. Antibiotic therapy is often adequate to treat the infection, though sometimes doctors also administer diphtheria antitoxin.

The INCUBATION PERIOD for either type of diphtheria is two to five days after exposure. The infection is contagious for up to two weeks after symptoms emerge. The course of uncomplicated illness is four to six weeks. Respiratory diphtheria (especially when untreated) may result in complications that include MYOCARDITIS (INFLAMMATION and infection of the HEART MUSCLE), NEURITIS, RESPIRATORY FAILURE, and death. Childhood immunization with booster vaccines every 10 years is the most effective means of prevention. Some people are carriers of *C. diphtheriae* bacteria, which requires human hosts for survival. Carriers have the infection present in their bodies but do not become ill, though they can pass the infection to others. ANTIBIOTIC PROPHYLAXIS prevents infection in people who are exposed to *C. diphtheriae*.

See also CHILDHOOD DISEASES; PREVENTIVE HEALTH CARE AND IMMUNIZATION.

encephalitis INFLAMMATION and INFECTION of the BRAIN. Encephalitis usually results from infection with a VIRUS and is potentially life threatening. Infection can enter the brain via pathogens that are small enough to pass across the BLOOD–BRAIN BARRIER or that are able to follow neural pathways (the routes of nerves) into the brain. The most common cause of encephalitis is infection with an arbovirus transmitted through the bite of a mosquito or tick. Other viruses that typically cause common infections may affect the brain to cause encephalitis, and encephalitis may develop as a complication of viral infection (and less commonly bacterial infection) elsewhere in the body. TOXOPLASMOSIS, a parasitic infection, may also cause encephalitis.

VIRUSES THAT CAN CAUSE ENCEPHALITIS

CYTOMEGALOVIRUS (CMV)	California VIRUS
eastern equine virus	EPSTEIN-BARR VIRUS
HERPES SIMPLEX virus (HSV)	LaCrosse virus
MUMPS virus	Powassan virus
RUBELLA virus	rubeola (MEASLES) virus
St. Louis virus	varicella zoster viruses
West Nile virus	western equine virus

Symptoms and Diagnostic Path

The symptoms of encephalitis differ somewhat in children and in adults. Children often become lethargic, confused, irritable, and sensitive to light;

older children may complain of severe HEADACHE. Adults often exhibit changes in mental alertness, cognitive ability, and emotional stability and may have severe headache. Both children and adults may have seizures, FEVER, NAUSEA, and VOMITING.

Diminished awareness or loss of consciousness that accompanies or follows other symptoms of encephalitis is an indication of serious INFECTION that requires urgent medical attention.

The diagnostic path includes LUMBAR PUNCTURE to determine the presence of pathogens or white BLOOD cells, or excessive fluid or increased pressure in the spinal column, any of which may indicate infection. Blood tests may show the presence of certain viruses. Diagnostic procedures such as electroencephalogram (EEG) and COMPUTED TOMOGRAPHY (CT) SCAN or MAGNETIC RESONANCE IMAGING (MRI) can show abnormalities of brain function and structure that are characteristic of encephalitis.

Treatment Options and Outlook

Mild viral encephalitis generally runs its course within five to seven days and does not require treatment beyond ANALGESIC MEDICATIONS such as acetaminophen to relieve fever and headache. ANTIVIRAL MEDICATIONS can reduce the severity of symptoms and length of illness for some forms of viral encephalitis, notably those resulting from viruses in the herpes family, though have no effect against encephalitis resulting from arboviruses. CORTICOSTEROID MEDICATIONS to suppress the inflammatory response can reduce intracranial swelling and pressure that commonly accompanies encephalitis. Bacterial encephalitis, which is much less common than viral encephalitis and usually a secondary infection, requires treatment with antibiotic medications. Antibiotics are not effective against viral infections.

Recovery depends on the severity of symptoms and the causative PATHOGEN. Though viral encephalitis is generally more mild than bacterial encephalitis, it can be fatal, particularly in infants, the very elderly, and people who are IMMUNOCOMPROMISED. People who have mild encephalitis recover completely and without residual complications. More severe illness may result in permanent brain damage and corresponding cognitive dysfunction, memory impairment, LEARNING DISORDERS, PARALYSIS, SEIZURE DISORDERS, or speech disorders.

Risk Factors and Preventive Measures

The risk for viral encephalitis is greatest during times of the year when mosquito and tick activity is highest, typically May through October in most parts of the United States. Other risks include living in close contact, such as in dormitories and institutions, and infection elsewhere in the body that migrates to the brain. Prevention efforts include public health measures to control mosquito populations and individual efforts to minimize exposure to mosquitoes and ticks.

See also COGNITIVE FUNCTION AND DYSFUNCTION; MEMORY AND MEMORY IMPAIRMENT; MENINGITIS.

Epstein-Barr virus A member of the herpesvirus family best known for causing the illness infectious mononucleosis. INFECTION with the Epstein-Barr VIRUS, also called human herpesvirus-4 (HHV-4), causes other disease as well and was the first virus researchers linked with cancer (notably Burkitt's lymphoma). Epstein-Barr virus is ubiquitous; it infects more than 90 percent of Americans by age 25.

As is characteristic of herpesvirus infections, Epstein-Barr virus causes first an acute illness (infectious mononucleosis), then retreats into a state of dormancy and remains in the body as a latent infection that does not cause illness or symptoms. B-cell lymphocytes, white BLOOD cells key to ANTIBODY-MEDIATED IMMUNITY, harbor the latent Epstein-Barr virus. Though the virus does not change the ability of its host B-cell lymphocytes to function within the IMMUNE RESPONSE, it does alter their DNA such that they become immortalized—they lose their genetic encoding for APOPTOSIS, the natural process for cell death.

Only a small percentage of B-cell lymphocytes contain the virus, so for the most part immune function continues as normal. A healthy IMMUNE SYSTEM maintains a balance between B-cell lymphocytes and T-cell lymphocytes (white blood cells key to CELL-MEDIATED IMMUNITY) that prevents B-

cell lymphocytes containing the latent Epstein-Barr virus from endlessly proliferating. As a result of this balance, in most people the virus never regains enough presence to again cause illness.

Circumstances that challenge the immune system allow the Epstein-Barr virus to reactivate. The most notable of these circumstances are HIV/AIDS and IMMUNOSUPPRESSIVE THERAPY after ORGAN TRANSPLANTATION. The reactivated Epstein-Barr virus may cause symptoms similar to infectious mononucleosis (chronic infectious mononucleosis) during which the person may spread the virus to others. It may also cause lymphoproliferative disorders: abnormal growth (tumors) of lymphatic structures such as lymph nodes and MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT). Though research is under way to develop a VACCINE to prevent infection with Epstein-Barr virus, at present there are no effective measures to prevent infection with the virus and no treatments to eradicate the virus once it establishes infection.

DISEASES ASSOCIATED WITH EPSTEIN-BARR VIRUS

acute infectious mononucleosis	AIDS-associated lymphoma
chronic infectious mononucleosis	Burkitt's lymphoma
nasopharyngeal CARCINOMA	generalized lymphoproliferative disease
	post-transplant lymphoproliferative disorder (PTLD)

See also B-CELL LYMPHOCYTE; CELL STRUCTURE AND FUNCTION; HERPES SIMPLEX; HERPES ZOSTER; KAPOSI'S SARCOMA; LYMPH NODE; LYMPHOCYTE; MONONUCLEOSIS, INFECTIOUS; OPPORTUNISTIC INFECTION; T-CELL LYMPHOCYTE.

***Escherichia coli* infection** Illness that results from INFECTION with any of the numerous strains of *Escherichia coli* BACTERIA, some of which are NORMAL FLORA in the human gastrointestinal tract and others that are normal flora in the gastrointestinal tracts of animals consumed as food (such as cattle and poultry). Most strains of *E. coli* cause mild to moderate illness. Illness from *E. coli* infection results from the toxins the *E. coli* release through their normal metabolic functions. The strain *E. coli* O157:H7, found in beef contaminated with fecal matter, can cause particularly severe illness.

Symptoms and Diagnostic Path

The symptoms of common *E. coli* infection are generally mild to moderate in severity and include

- abdominal cramping
- DIARRHEA
- occasionally NAUSEA and VOMITING

The symptoms of *E. coli* O157:H7 infection are often more severe and include ABDOMINAL PAIN with profuse, sometimes bloody diarrhea. Though most people recover fully after the illness runs its course in 5 to 10 days, in some people the toxins the *E. coli* O157:H7 release cause the massive destruction of red BLOOD cells (erythrocytes), a process called HEMOLYSIS. The enormous volume of dead erythrocytes creates proteins in the blood that are damaging to the KIDNEYS, resulting in RENAL FAILURE. The combination of these circumstances is HEMOLYTIC UREMIC SYNDROME (HUS), which occurs as a complication of *E. coli* O157:H7 infection in about 5 percent of people (mostly children under age 5). HUS nearly always results in END-STAGE RENAL DISEASE (ESRD), requiring dialysis or KIDNEY TRANSPLANTATION.

The diagnostic path for *E. coli* infection may include culture of stool samples to determine the causative PATHOGEN, though most often doctors do this only when the illness continues beyond about two weeks or has severe symptoms. The doctor must specifically request culture for *E. coli* O157:H7 as most laboratories do not routinely include this in their testing.

Treatment Options and Outlook

E. coli diarrheal illnesses are very common and nearly all people who acquire them fully recover in three to five days without treatment, except fluid replacement to prevent DEHYDRATION. ANTIBIOTIC MEDICATIONS are seldom appropriate because the cause of symptoms is the toxins the *E. coli* bacteria release, and killing the bacteria causes them to release even more toxins. It is sometimes helpful to avoid dairy products until bowel activity returns to normal. People who become seriously ill with *E. coli* O157:H7 may require care in the hospital. Though *E. coli* O157:H7 infection has gained substantial notoriety, more than 95 percent

of people who become ill with it recover without complications.

Risk Factors and Preventive Measures

E. coli infections result from contaminated water or food, especially meats. Swimming in lakes and rivers often exposes people to *E. coli* contamination; swallowing the water allows the bacteria to enter the gastrointestinal system. Most *E. coli* infections are FOODBORNE ILLNESSES.

Preventive measures include

- diligent HAND WASHING
- following FOOD SAFETY guidelines for handling and preparing meats and other foods
- thoroughly cooking meats, especially ground beef

Most *E. coli* infections are preventable.

See also ERYTHROCYTE; WATERBORNE ILLNESSES.

F–G

fever An elevation of body temperature above the normal range. Body temperature varies over the course of a circadian cycle, roughly equivalent to 24 hours, to accommodate the body's metabolic needs. Body temperature is lowest just before waking in the morning and highest in the late afternoon or early evening, times that typically correlate with the body's lowest and highest expenditures of energy. The normal range of body temperature is 97.6°F to 99.6°F, with the mean of 98.6°F generally perceived as the standard normal temperature. Health-care providers generally view a body temperature of 100°F or higher as a fever.

The body's IMMUNE RESPONSE raises body temperature as a mechanism for fighting INFECTION. Elevated body temperature increases the body's METABOLISM, which enhances the IMMUNE SYSTEM's ability to contain and eradicate the pathogens responsible for infection. Each degree of elevation in body temperature accelerates metabolism by 10 to 15 percent. The various types of white BLOOD cells (leukocytes) release INTERLEUKINS, PROSTAGLANDINS, TUMOR NECROSIS FACTORS (TNFS), and other biochemicals (CHEMOKINES) that temporarily reset the body's thermoregulatory mechanisms.

Though common practice is to attempt to lower a fever through measures such as cool baths and acetaminophen or other medications, doctors now believe fever does not ordinarily require treatment. To the contrary, recent research shows that the immune response and most ANTIBIOTIC MEDICATIONS work more effectively when body temperature is elevated. Doctors recommend treating fever only when there is risk for febrile seizures, when the person cannot eat or drink enough to meet the body's metabolic needs, or when the fever creates discomfort. Medications to treat other symptoms due to the infection, such as HEADACHE, also reduce fever.

See also ANALGESIC MEDICATIONS; HEAT EXHAUSTION; HEAT STROKE; LEUKOCYTE; NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS); PATHOGEN.

foodborne illnesses Diseases resulting from consumption of foods contaminated with pathogenic BACTERIA, fungi, parasites, or viruses. Foodborne illnesses, also called food poisoning, are common, affecting 76 million Americans each year. There are several hundred known foodborne illnesses, most of which cause mild to moderate gastrointestinal symptoms including abdominal cramping, NAUSEA, VOMITING, and DIARRHEA. Illness results from consuming a food contaminated with pathogens. Common sources include undercooked meats and cooked foods that remain at room temperature for longer than two hours. Most often, it is not possible to tell from taste, smell, or appearance that a food contains pathogens.

Prevention is the primary focus when it comes to foodborne illnesses. The simple measure of washing the hands before and after preparing foods, eating meals, changing diapers, and using the bathroom could eliminate many foodborne illnesses by preventing bacteria and other pathogens from contact with foods. Other FOOD SAFETY measures to reduce the risk for infection from foodborne pathogens include

- using separate utensils and surfaces for meats and for other foods
- washing fruits and vegetables, including "rind" fruits such as oranges and watermelon, in running water before eating or preparing them

- thoroughly cooking all animal-based foods (including eggs), to 160ºF for most meats and poultry (no pink in the flesh)
- prompt refrigeration of leftover foods

Most foodborne illnesses are self-limiting; the infection runs its course (usually within three to five days) and the person fully recovers without medical treatment. Supportive treatment such as adequate fluid intake is important to prevent DEHYDRATION; soups and juices also help maintain nutrition. Doctors often discourage people from taking ANTIDIARRHEAL MEDICATIONS that work by slowing gastrointestinal motility, such as loperamide or diphenoxylate, because these drugs may prolong the illness by prolonging the presence of the PATHOGEN in the gastrointestinal tract.

Some foodborne illnesses need prompt medical treatment, such as BOTULISM. Some parasitic and bacterial infections require appropriate medications. Some foodborne illnesses may spread from one person to another, such as HEPATITIS and *ESCHERICHIA COLI* INFECTION. A doctor should evaluate symptoms that are severe or persist longer than five days.

FOODBORNE ILLNESSES

AMEBIASIS	BOTULISM
CAMPYLOBACTERIOSIS	*Escherichia coli* INFECTION
GIARDIASIS	HEPATITIS
LISTERIOSIS	Norwalk-like virus
SALMONELLOSIS	SHIGELLOSIS
TOXOPLASMOSIS	

See also FUNGUS; PARASITE; VIRUS; WATERBORNE ILLNESSES.

fungus Any of the 200,000 or so of single or multiple cell organisms (living structures), microscopic (visible only using a microscope for magnification) and macroscopic (visible to the unaided EYE), that are abundant in the natural environment. Yeasts are single-cell fungi that live in colonies; molds are multiple-cell fungi that form structures. Like BACTERIA, fungi are among the oldest life forms to inhabit the Earth; fossils of yeasts date back more than 2 billion years.

Most fungi are harmless to humans and many are NORMAL FLORA (present in body and on the SKIN). Fungi break down organic waste; yeasts, for example, populate the gastrointestinal tract where they aid in digestion. Many ANTIBIOTIC MEDICATIONS derive from fungi, notably penicillin (first cultivated from the mold *Penicillium chrysogenum*).

Some fungi are pathogenic (disease causing) in people under any circumstances and others cause OPPORTUNISTIC INFECTION in people who are IMMUNOCOMPROMISED. Fungal diseases may be localized, such as ONYCHOMYCOSIS (fungal INFECTION of the nail beds), or systemic, such as HISTOPLASMOSIS. Doctors use ANTIFUNGAL MEDICATIONS to treat fungal infections that cause disease.

FUNGAL DISEASES

ASPERGILLOSIS	blastomycosis
CANDIDIASIS	COCCIDIOIDOMYCOSIS
CRYPTOCOCCOSIS	HISTOPLASMOSIS
mucormycosis	ONYCHOMYCOSIS
sporotrichosis	tinea barbae (ringworm)
tinea capitis (ringworm)	tinea corporis (ringworm)
tinea cruris (jock itch)	tinea pedis (athlete's foot)

Fungi may also be a source of poisoning. *Aspergillus* molds on grains produce aflatoxins, for example, which cause LIVER damage and are associated with LIVER CANCER. Many types of mushrooms produce toxins (mycotoxins) that cause illness or death when eaten, such as the highly toxic "death cap" mushroom, *Amanita phalloides*. Molds may grow in buildings where humidity and darkness converge to provide the ideal environment for their growth, such as inside walls and floors where there have been water leaks. The spores of these fungi cause respiratory illnesses and other health problems when breathed in with the air, particularly for people who have ASTHMA or other chronic pulmonary conditions.

See also BUILDING-RELATED ILLNESS; INDOOR AIR QUALITY; MICROBE; OCCUPATIONAL HEALTH AND SAFETY; PARASITE; PATHOGEN; PROTOZOA; TINEA INFECTIONS; VIRUS.

genital herpes A sexually transmitted disease (STD) resulting from INFECTION with herpesvirus, usually HERPES SIMPLEX VIRUS 2 (HSV-2). Herpes

simplex virus 1 (HSV-1), which causes cold sores, may also cause sores in the genital area. Genital herpes is one of the most prevalent STDs in the United States, infecting about 25 percent of teens and adults—more than 45 million people. About 1 million new infections occur each year.

As is characteristic of the herpesviruses, HSV-2 remains in the body for life after the initial infection, retreating to NERVE roots within the areas of infection. Periodically the virus travels along the nerves to the surface of the SKIN, causing outbreaks of blisters that become crusted sores. During these outbreaks the virus both replicates and sheds, and the infected person is highly contagious. Such a pattern of REMISSION and RECURRENCE continues through life; there currently is no cure for genital herpes.

Direct contact with SEMEN, vaginal fluids, and saliva spreads genital herpes from one person to another during vaginal intercourse, anal intercourse, or oral sex. The infection does not spread via contact with objects such as toilet seats or in water (such as swimming pools and hot tubs). Genital herpes is contagious even when no sores are present. Because symptoms may be mild, or in women occur within the VAGINA, many people do not know they have genital herpes. The first outbreak of symptoms tends to be the most severe. Over time outbreaks tend to become less frequent with fewer and smaller sores.

Symptoms and Diagnostic Path

Symptoms, when they occur, begin about two weeks after sexual contact with an infected person who is shedding the virus. Initial symptoms may include

- tingling, burning, or pain at the site of infection (PENIS, vagina, CERVIX, ANUS, RECTUM, MOUTH, and sometimes on skin surfaces)
- FEVER
- HEADACHE
- swollen LYMPH nodes near the site of the infection
- vaginal discharge in women
- painful URINATION in men

The hallmark symptom of genital herpes is painful sores that begin as red bumps that BLISTER and then crust. The sores appear at the sites where the virus entered the body and are usually most severe with the first outbreak. Symptoms of subsequent outbreaks tend to be more mild, though sores may appear in new locations as the virus spreads along nerve paths. The sores are present for three to four weeks and then heal without scarring. Periods of remission during which there are no sores or other symptoms may last several weeks to several months.

Health-care providers generally presume a diagnosis of genital herpes when the characteristic sores are present in a person who is sexually active. BLOOD tests can detect the presence of HSV antibodies but this is not especially useful information from a diagnostic perspective because more than 90 percent of people have some sort of herpesvirus infection—herpes simplex, HERPES ZOSTER, varicella (CHICKENPOX)—that activates the ANTIBODY response and blood tests cannot distinguish among the type of herpesvirus present. Cultures of the sores may produce HSV-2, which confirms the diagnosis. However, cultures of the sores may sometimes be negative even when HSV-2 infection is present.

Treatment Options and Outlook

The sores that erupt during a genital herpes outbreak will heal without treatment within two or three weeks. ANTIVIRAL MEDICATIONS can shorten the length of the outbreak and reduce the number and severity of the sores. Some people benefit from taking an antiviral medication daily, which may lessen the frequency of outbreaks. Valacyclovir is the medication doctors most commonly prescribe for regular use. Antiviral medications do not cure genital herpes, however.

ANTIVIRAL MEDICATIONS TO TREAT GENITAL HERPES

acyclovir	famciclovir	valacyclovir

Most people who have genital herpes experience outbreaks of symptoms several times a year. Stress, MENSTRUATION, and other viral infections such as COLDS seem to trigger outbreaks though symptoms may erupt without apparent cause. The open sores of genital herpes create increased risk for infection with HIV. A pregnant woman can pass genital herpes to her unborn child; doctors

may recommend CESAREAN SECTION (surgical delivery) for women whose infections are active (symptomatic) near the time of delivery to prevent this.

Risk Factors and Preventive Measures

Because HSV-2 infection is so prevalent, all sexually active people are at risk for genital herpes. Uninfected people who are in monogamous relationships with uninfected sexual partners have the lowest risk for infection; uninfected people who have multiple sexual partners or who are in relationships with sexual partners who have genital herpes have the highest risk for infection. At present the most effective means of prevention among sexually active adults is abstinence during outbreaks and barrier protection such as latex condoms during all sexual activity. Barrier protection is not absolute, however, as the HSV-2 virus may infect nerve cells at the skin's surface that the condom does not cover.

The antiviral medication valacyclovir significantly reduces viral shedding, slowing but not entirely preventing transmission of genital herpes. This preventive measure is most effective in monogamous relationships in which one person has HSV-2 and the other does not. Clinical studies are under way to evaluate a vaccine for genital herpes.

See also CHLAMYDIA; COLD SORE; CONTRACEPTION; GONORRHEA; HUMAN PAPILLOMAVIRUS (HPV); LYMPH NODE; OCULAR HERPES; SEXUAL HEALTH; SEXUALLY TRANSMITTED DISEASE (STD) PREVENTION; SEXUALLY TRANSMITTED DISEASES (STDS); SYPHILIS.

giardiasis An illness resulting from INFECTION with the protozoan *Giardia lamblia* (also called *Giardia intestinalis*). *Giardia* are abundant in fresh water throughout the United States; infection occurs through drinking contaminated water. The PROTOZOA infect the SMALL INTESTINE of humans and animals and can survive for extended periods without a host. The most common means of infection is through swallowing water in recreational settings, such as lakes, rivers, and streams. Fountains, swimming pools, and hot tubs that lack proper chlorination also may harbor *Giardia*. Giardiasis also spreads through fecal contamination by direct contact, such as by changing diapers, and can occur as a FOODBORNE ILLNESS spread through poor FOOD SAFETY practices.

Symptoms develop after an incubation period of 7 to 10 days and include DIARRHEA, excessive FLATULENCE (gas), abdominal discomfort, and NAUSEA. The diarrhea is watery and has a greasy appearance. Some people also experience fatigue, loss of APPETITE, and rapid weight loss. It is also possible to have giardiasis and have no symptoms. Stool samples examined under the microscope typically contain both cysts and trophozoites, the immature and mature forms, respectively, of the *Giardia*. Treatment is ANTIBIOTIC MEDICATIONS and ANTIFUNGAL MEDICATIONS. The course of illness runs four to six weeks with treatment, after which most people recover without complications or residual consequences. Without treatment giardiasis may persist for six to eight weeks, with gradual though complete recovery.

MEDICATIONS TO TREAT GIARDIASIS

albendazole	furazolidone
metronidazole	nitazoxanide
paromomycin	tinidazole

See also AMEBIASIS; BABESIOSIS; DRINKING WATER STANDARDS.

gonorrhea A sexually transmitted disease (STD) resulting from INFECTION with the bacterium *Neisseria gonorrhoeae*. *N. gonorrhoeae* infects 350,000 Americans each year, though public health officials believe another 350,000 people have gonorrhea that goes undiagnosed because they do not know they are infected. Gonorrhea is highly contagious and passes among sexual partners through vaginal intercourse, anal intercourse, or oral sex. People who have multiple sex partners have increased risk for gonorrhea as well as other STDs. Gonorrhea is a public health concern of great magnitude worldwide because a number of strains of *N. gonorrhoeae* have become resistant to the ANTIBIOTIC MEDICATIONS used to treat the infection.

Symptoms and Diagnostic Path

Gonorrhea has a 2- to 10-day INCUBATION PERIOD (time from exposure to symptoms) though often causes no symptoms, especially in women. Symptoms that do occur tend to be generalized and

vague, such as lower abdominal discomfort, and go away in a few days to a week. When symptoms are present they typically include

- a thick, discolored (yellowish or greenish), or bloody discharge from the PENIS in men and the VAGINA in women
- burning or PAIN with URINATION (more common in men)
- pain or bleeding during SEXUAL INTERCOURSE (more common in women)

Early symptoms will go away without treatment, though the infection remains. As the *N. gonorrhoeae* BACTERIA multiply in the body, they cause increasing irritation to the tissues, resulting in INFLAMMATION and the formation of SCAR tissue. In men the next level of infection with untreated gonorrhea is EPIDIDYMITIS, which causes swelling and pain in the TESTICLES, and URETHRITIS, which causes intense pain with urination. In women the next level of infection with untreated gonorrhea is PELVIC INFLAMMATORY DISEASE (PID), which involves the UTERUS and FALLOPIAN TUBES. PID often causes severe ABDOMINAL PAIN. Scarring from the infection blocks the fallopian tubes, putting a woman at high risk for ECTOPIC PREGNANCY.

Diagnosis is laboratory examination of a sample of the discharge taken from the penis (men) or the CERVIX (women). A fast test done in the doctor's office is highly accurate for men but not for women; for women, a conventional culture is the most reliable diagnostic procedure. The doctor likely will conduct diagnostic tests for other STDs as well, notably CHLAMYDIA and SYPHILIS. All sex partners should also undergo testing and receive treatment if they have gonorrhea, even if they do not have symptoms.

Treatment Options and Outlook

The current standard of treatment for gonorrhea is a single DOSE of a fluoroquinolone antibiotic, which cures the infection in most people. However, new strains of *N. gonorrhoeae* are showing resistance to these antibiotics, causing doctors to look to combinations of antibiotics and to stronger antibiotics to cure the infection.

ANTIBIOTIC MEDICATIONS TO TREAT GONORRHEA

azithromycin	cefixime
ceftriaxone	ciprofloxacin
levofloxacin	ofloxacin

The debut of penicillin in the 1940s provided the first cure for gonorrhea. However, 30 years later, most strains of *N. gonorrhoeae* were resistant to penicillin and to tetracycline, the second-choice antibiotic. Doctors can no longer prescribe these antibiotics to treat gonorrhea. Though antibiotic medications remain the standard of treatment for gonorrhea, doctors and public health officials worry that the ability of *N. gonorrhoeae* to adapt will soon put gonorrhea out of reach for treatment. Researchers have recently unraveled the GENETIC CODE (DNA sequence) of the *N. gonorrhoeae* and are hopeful this advance will lead to new kinds of treatments.

Risk Factors and Preventive Measures

Those who are at highest risk for gonorrhea and other STDs are

- women between the ages of 15 and 19
- men between the ages of 20 and 24
- men who have sex with men
- men or women who have multiple sex partners

Monogamy (having only one sex partner) and consistent use of latex condoms are measures that can prevent *N. gonorrhoeae* infection. People who are sexually active should undergo regular testing for STDs. Reinfection can occur.

See also ANTIBIOTIC RESISTANCE; GENITAL HERPES; HIV/AIDS; HUMAN PAPILLOMAVIRUS (HPV); SEXUAL HEALTH; SEXUALLY TRANSMITTED DISEASE (STD) PREVENTION; SEXUALLY TRANSMITTED DISEASES (STDS).

hantavirus pulmonary syndrome An illness resulting from INFECTION with hantavirus. Certain species of deer mice carry the hantavirus, which they shed in their droppings, URINE, and saliva. People who come into contact with these excretions, which may be through direct touch or inhalation, may then acquire infection with the VIRUS. Deer mice live primarily in wooded areas. Most often a person acquires the infection after cleaning in barns and outbuildings where mouse droppings can accumulate; the cleaning stirs up dust that carries the virus into the respiratory tract. People who go camping in areas where there are large populations of deer mice also are at risk for infection.

The INCUBATION PERIOD (time between exposure and illness) is one to three weeks. Symptoms emerge abruptly and include FEVER, severe MUSCLE aches (particularly in the large muscles of the legs and back), and shortness of breath (DYSPNEA) that rapidly progresses to respiratory failure. A BLOOD test can show the presence of antibodies to confirm the diagnosis. Treatment is hospitalization, usually in an intensive care unit, to provide support for BREATHING while the virus runs its course. Hantavirus pulmonary syndrome is a very serious infection with a high fatality rate. Early, aggressive medical support offers the best potential for successful recovery.

See also ANTIBODY; HEMORRHAGIC FEVERS; MECHANICAL VENTILATION.

hemorrhagic fevers Life-threatening illness resulting from INFECTION with various viruses, spread by the bites of mosquitoes and ticks, the hallmark of which is the collapse of multiple organ systems because damage to the BLOOD vessels impairs their ability to contain and transport blood. The dozen or so viruses that cause hemorrhagic fevers belong to four viral families: arenaviruses, bunyaviruses, filoviruses, and flaviviruses. These viral families also contain viruses that cause infection other than hemorrhagic FEVER. For example HANTAVIRUS belongs to the bunyavirus family and the yellow fever VIRUS belongs to the flavivirus family. Viral hemorrhagic fever infections occur in tropical regions, notably Africa and South America.

HEMORRHAGIC FEVER VIRUSES	
Arenaviruses	
Guanarito VIRUS	Junin virus
Lassa virus	Machupo virus
Sabia virus	
Bunyaviruses	
Crimean-Congo virus	Rift Valley virus
Filoviruses	
Ebola virus	Marburg virus
Flaviviruses	
Dengue virus	Omsk virus

Rodents, primarily certain species of rats and mice, harbor the viruses. Mosquitoes and ticks that feed on the rodents continue to spread the virus among rodent populations. Rodent droppings and other excretions, such as saliva and URINE, contain the viruses. The viruses can then infect people who come into contact with the excretions. Contact with body fluids from an infected person further spread the virus. Symptoms of illness arise suddenly and are severe, typically including high fever, fatigue, evidence of internal bleeding, and weakness. Subsequent

symptoms develop as organs fail. The only treatment for viral hemorrhagic fevers is supportive; the illnesses are usually fatal. Outbreaks of viral hemorrhagic fevers occur periodically. Global efforts are under way to find medical treatments that can halt the course of disease as well as to contain rodent, mosquito, and tick populations.

See also COMMUNITY SANITATION.

herpes simplex INFECTION with the herpes simplex VIRUS 1 (HSV-1) or HSV-2. HSV-1 primarily causes cold sores on the lips and in the MOUTH, transmitted through saliva. HSV-2 primarily causes GENITAL HERPES, a sexually transmitted disease (STD) that causes ulcerative sores on the genitals. However, either form of the virus can cause infection anywhere in the body. HSV-1 and HSV-2, like other herpes viruses, are highly contagious through contact with the sores and may also spread from one person to another even when no sores are present. Herpes simplex infection is lifelong, though symptoms characteristically wax and wane. About 90 percent of Americans have HSV-1 and about 30 percent have HSV-2.

The typical course of an outbreak begins with itching or tingling, called the prodrome, which gives way to the eruption of a BLISTER within 48 hours. Cold sores typically form as single blisters though may occur as multiple blisters in several locations; genital herpes sores tend to erupt in clusters. After two or three days the blisters rupture and form crusted sores that subsequently heal. The cycle from prodrome to HEALING lasts about 10 days. Because the course of illness is so characteristic, the doctor can usually make the diagnosis on the appearance of the sores. Laboratory culture of the fluid within a blister or sore can provide a definitive diagnosis.

After an outbreak of symptoms the virus retreats to the local NERVE roots where it remains dormant until the next outbreak. Researchers are not certain what factors initiate outbreaks though stress and exposure to sunlight appear to play key roles. Doctors sometimes prescribe ANTIVIRAL MEDICATIONS such as acyclovir for people who have six or more outbreaks of herpes simplex infection in a year or who have severe symptoms during outbreaks. Herpes infections may involve the eyes or the BRAIN, where they can cause permanent damage.

See also CANKER SORE; CHICKENPOX; COLD SORE; HERPES ZOSTER; SEXUALLY TRANSMITTED DISEASE (STD) PREVENTION; SEXUALLY TRANSMITTED DISEASES (STDS).

herpes zoster An INFECTION that results from reactivation of the varicella-zoster VIRUS, which lies dormant in the spinal NERVE roots after causing CHICKENPOX. The virus can remain dormant for decades; doctors do not know what reactivates it though suspect a combination of aging and stress to the IMMUNE SYSTEM. The infection travels the tract of a spinal nerve to the SKIN, causing burning or PAIN as it makes its way to the body's surface. Called the prodrome, this discomfort yields in about two days to a rash of painful blisters that erupts along the nerve's pathway, called a DERMATOME. The blisters rupture in three to five days and crusted sores form at the sites of the blisters.

Herpes zoster, also called shingles, occurs only on one side of the body, most commonly on the chest though may affect dermatomes anywhere on the body. The blisters of the herpes zoster outbreak can spread the virus, which can cause chickenpox in people who have not had it or have not received the varicella VACCINE. An uncomplicated outbreak of herpes zoster runs its course in three to four weeks, after which the virus again goes dormant. Treatment with an antiviral medication taken at the onset of pain but before blisters emerge (the prodrome) can significantly shorten the course of illness and decrease the severity of symptoms.

ANTIVIRAL MEDICATIONS TO TREAT HERPES ZOSTER

acyclovir	desciclovir
famciclovir	penciclovir
valacyclovir	

Complications after the outbreak abates may include damage to the eyes, loss of taste, and partial PARALYSIS of the face when the outbreak involves the trigeminal nerve. Post-herpetic NEURALGIA is pain that persists along the dermatome after the sores have completely healed, and may be debilitating. Unlike its predecessor infection, chickenpox, herpes zoster can recur though usually does not.

See also AGING, EFFECTS ON IMMUNE RESPONSE; BLISTER; GENITAL HERPES; HERPES SIMPLEX; SPINAL NERVES.

histoplasmosis An illness resulting from INFECTION with the FUNGUS *Histoplasma capsulatum*. This fungus, commonly called a mold, thrives in soils where bird droppings are abundant, such as chicken farms, barns where pigeons and starlings nest, and caves where bats roost. Histoplasmosis is endemic (continuously present) in the river valley areas of the central United States, where the rich and acidic soil provides an especially supportive environment for fungi to grow.

When inhaled, the *H. capsulatum* spores cause lesions in the LUNGS. An acute infection causes symptoms only in about 10 percent of people, though nonetheless can do considerable damage to lung tissue. Permanent scarring (granulomas and cavitations) often occurs in untreated histoplasmosis. Chronic histoplasmosis may develop in people who have underlying pulmonary disease or repeated exposure to *H. capsulatum* spores. The most significant risk of histoplasmosis is disseminated disease, in which the spores enter the BLOOD circulation and migrate to other organs throughout the body. Disseminated histoplasmosis, often an OPPORTUNISTIC INFECTION in people who have HIV/AIDS or are otherwise IMMUNOCOMPROMISED, has a high rate of fatality.

Symptoms and Diagnostic Path

Symptoms in acute histoplasmosis generally appear within two weeks of exposure and include

- FEVER
- HEADACHE
- JOINT PAIN
- MUSCLE aches
- nonproductive (dry) COUGH

People who inhale a large quantity of the spores may have extensive lung involvement that causes shortness of breath (DYSPNEA). The diagnostic path begins with a detailed personal health history with emphasis on exposure to bird droppings, blood tests, and a SKIN ANTIGEN test. Chest X-RAY reveals the characteristic histoplasmosis lesions, and may also show enlarged LYMPH nodes in the chest (hilar and mediastinal LYMPHADENOPATHY).

Treatment Options and Outlook

Acute histoplasmosis usually resolves without treatment, running a course much like that of a common upper respiratory infection. Bacterial PNEUMONIA may occur as a complication of acute histoplasmosis, requiring treatment with ANTIBIOTIC MEDICATIONS. Doctors prescribe ANTIFUNGAL MEDICATIONS to treat moderate to severe acute symptoms, chronic histoplasmosis, and disseminated histoplasmosis. With appropriate treatment, most people who have normal immunocompetence recover though residual lung damage is possible. Chronic and disseminated forms of infection often require long-term or lifelong treatment with antifungal medications.

ANTIFUNGAL MEDICATIONS TO TREAT HISTOPLASMOSIS

amphotericin B	itraconazole	ketoconazole

Risk Factors and Preventive Measures

People who work with live poultry or in outdoor areas that have large bird populations have increased risk for infection with *H. capsulatum*. Minimizing disturbance of the soil helps reduce the release of spores into the air. People who work in areas where exposure is a risk should wear respirators. Recreational activities in areas where birds or bats are common may also be a risk for exposure.

See also HANTAVIRUS; LESION.

HIV/AIDS An INFECTION with the human immunodeficiency virus (HIV) that ultimately results in the illness acquired immunodeficiency syndrome (AIDS). Though new HIV/AIDS infections are on the decline in the United States and other industrialized nations, HIV/AIDS remains endemic on the African continent.

HIV/AIDS spreads through contact with body fluids such as occurs with sexual contact (vaginal intercourse, anal intercourse, and oral sex) or through shared needles among intravenous DRUG users. Though previously infection through transfused BLOOD or blood products was a key means of infection, screening for HIV antibodies in donated

blood supplies has significantly reduced this risk and infection through blood products is now uncommon.

Though there are numerous treatments for HIV/AIDS, there is no cure. HIV, the infection, nearly always progresses to AIDS, the illness, over the course of 5 to 20 years. Aggressive treatment can further manage the symptoms and complications of AIDS for years to sometimes decades. However, AIDS is ultimately fatal. AIDS does not itself cause death but instead so extensively damages the IMMUNE SYSTEM, the infection's target, that the body cannot protect itself from infections or conditions such as cancer, which become the causes of death.

The Virus: HIV

The human immunodeficiency virus, HIV, is a retrovirus that exists in two known types, HIV-1 and HIV-2. Each infects the body in the same way and etches the same pathway to AIDS. HIV-1 is predominant in North America and Europe; HIV-2 is predominant in Africa, Southeast Asia, and China. HIV enters the body by attaching itself to a type of T-CELL LYMPHOCYTE called a CD4 cell (helper T-cell). CD4 cells direct the immune system's response to infection and are integral to CELL-MEDIATED IMMUNITY. Once attached, the HIV virion, the essential structure of the VIRUS before it acquires a host cell, can infiltrate the cell without the immune system detecting its presence.

As a retrovirus, HIV uses reverse transcriptase, an enzyme, to instruct the CD4 cell's RNA to replicate the virus's RNA in place of the cell's DNA. The cell then supports and replicates the virus, releasing new virions to infect additional CD4 cells. The entire process is quite stealthy. Therapeutic interventions are not quite of comparable stealth, though are getting closer to the mark. For example, ANTIVIRAL MEDICATIONS called nucleoside analogs can interject themselves into the process of reverse transcription, with the result that the cell produces "blank" DNA that fails to replicate the virus.

The Illness: AIDS

The ultimate outcome, at present, of HIV infection is the collapse of the immune system. Eventually the number of CD4 cells under HIV control is significantly greater than the number of CD4 cells under control of the immune system. Critical mass shifts and the immune system becomes deficient: It lacks the resources to rally against even the most minor of infections. Illness ranging from CANDIDIASIS (yeast infection) to AIDS-related lymphoma (a type of cancer) takes over. It is these illnesses, not HIV/AIDS, that causes death.

Symptoms and Diagnostic Path

About two weeks after infection with HIV, mild flulike symptoms appear that last 10 to 14 days. Most people do not recognize these symptoms as HIV infection. After these initial symptoms resolve, there are no further symptoms until AIDS emerges. However, HIV antibodies become present in the body three to six months after infection (called seroconversion). Various tests are available to detect the presence of HIV antibodies, which confirm that a person has HIV infection (is HIV-positive). HIV infection is not the same as AIDS. AIDS is the end-stage outcome of HIV infection. At present the diagnostic criteria for the transition from HIV infection to AIDS is a CD4 count below 200 cells per cubic millimeter (mm^3) and/or the development of an AIDS-defining clinical conditions (an illness that a healthy immune system would block from occurring).

AIDS-DEFINING CLINICAL CONDITIONS

AIDS-associated lymphoma	Burkitt's lymphoma
CANDIDIASIS	chronic HERPES SIMPLEX
COCCIDIOIDOMYCOSIS	CRYPTOCOCCOSIS
CRYPTOSPORIDIOSIS	CYTOMEGALOVIRUS (CMV) disease or retinitis
HISTOPLASMOSIS	invasive CERVICAL CANCER
HIV-related ENCEPHALOPATHY	KAPOSI'S SARCOMA
isosporiasis	*Pneumocystis carinii* PNEUMONIA
Mycobacterium avium complex	*Salmonella* SEPTICEMIA, recurrent
progressive multifocal leukoencephalopathy	TUBERCULOSIS
TOXOPLASMOSIS of brain	
wasting syndrome due to HIV	

Treatment Options and Outlook

There are numerous treatment protocols for HIV/AIDS that extend both life expectancy and QUALITY OF LIFE. Early HIV infection does not require treatment beyond lifestyle measures to stay as healthy as possible. As the HIV begins to

compromise the immune system, aggressive treatment with a regimen called HAART (highly active antiretroviral therapy), which combines three or more medications taken daily, can delay the progression of infection. Three factors influence the decision to begin HAART:

- CD4 count (the number of CD4 T-lymphocytes in the blood circulation) below 350 cells per cubic millimeter (mm^3)
- viral load (the number of copies of HIV in the blood circulation) above 100,000 per milliliter (ml)
- presence of symptoms or an AIDS-defining clinical condition

Doctors wait to start HAART until these conditions exist because the antiretroviral drugs have potentially serious side effects, necessitating a careful balance between benefit and risk, and because once started, treatment is lifelong.

ANTIRETROVIRAL DRUGS TO TREAT HIV/AIDS (HAART)

Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
delavirdine	efavirenz	nevirapine
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
abacavir	didanosine	emtricitabine
lamivudine	stavudine	tenofovir
zalcitabine	zidovudine	
Protease Inhibitors (PIs)		
amprenavir	atazanavir	fosamprenavir
indinavir	lopinavir	nelfinavir
ritonavir	saquinavir	tipranavir
Fusion Inhibitors		
enfuvirtide		

Regular blood tests to monitor CD4 counts and viral load determine how well a particular drug combination is working. Because drug toxicity and resistance are both problems with long-term HAART, it is sometimes necessary to change regimens.

Risk Factors and Preventive Measures

Numerous risk factors exist for HIV/AIDS. Key among them are

- unprotected vaginal intercourse, anal intercourse, or oral sex
- multiple sexual partners
- intravenous drug use with shared needles
- infection with SEXUALLY TRANSMITTED DISEASES (STDS) that have open sores, such as SYPHILIS and GENITAL HERPES
- vaginal intercourse during MENSTRUATION

Use of condoms with all sexual activity reduces the risk for spreading the virus but does entirely prevent infection. Pregnant women who are HIV-positive should discuss prophylactic treatment during PREGNANCY and for the infant after birth.

See also ANTIBODY; ANTIBODY-MEDIATED IMMUNITY; HIV/AIDS PREVENTION; SEXUAL HEALTH; SEXUALLY TRANSMITTED DISEASE (STD) PREVENTION.

human ehrlichiosis Any of several illnesses resulting from INFECTION with various species of *Ehrlichia* BACTERIA. Human ehrlichiosis infection spreads via tick bites. The tick species and the *Ehrlichia* species vary by geographic region. *Ehrlichia* bacteria infect white BLOOD cells. The two main forms of human ehrlichiosis in the United States are human granulocytic ehrlichiosis (hGE), in which the infection involves granulocytes (primarily neutrophils), and human monocytic ehrlichiosis (hME), in which the bacteria infect monocytes and macrophages. hME is about twice as common as hGE.

The INCUBATION PERIOD for human ehrlichiosis is 5 to 10 days, after which symptoms appear that are flulike in nature. Symptoms may include

- FEVER
- HEADACHE and general sense of not feeling well (malaise)
- JOINT PAIN and MUSCLE aches
- NAUSEA, VOMITING, and DIARRHEA

The diagnostic path includes blood tests to evaluate blood cell counts. The bacteria are also apparent with microscopic examination of a blood sample. *Ehrlichia* bacteria are highly sensitive to doxycycline, an antibiotic in the tetracycline family of ANTIBIOTIC MEDICATIONS. Because blood test results may take a week or longer, responsiveness

to antibiotic therapy is often a diagnostic measure. People who have human ehrlichiosis show marked improvement in symptoms within 24 to 36 hours of beginning doxycycline treatment. Most people recover fully with appropriate treatment. Though some people develop mild illness with few symptoms and fully recover without treatment, untreated human ehrlichiosis can become very serious very quickly because the attack on the white blood cells compromises immune function.

The risk for *Ehrlichia* infection in the United States is highest during the summer months (May through October) when people are hiking and camping in areas where ticks thrive. Measures to prevent tick bites include wearing protective clothing (such as long pants tucked into socks) or using an appropriate insect repellent and checking the SKIN carefully for ticks or signs of bites after being in wooded areas.

See also GRANULOCYTE; MACROPHAGE; MONOCYTE; ROCKY MOUNTAIN SPOTTED FEVER.

human papillomavirus (HPV) A family of more than 100 strains of VIRUS, various strains of which cause common WARTS, genital HPV infection, and CERVICAL CANCER.

HPV and Common Warts

The strains of HPV that cause common warts are mildly contagious and are more likely to spread to different locations on a person's body rather than to other people. These strains include

- HPV-2, HPV-4, and HPV-7, which cause the raised, rounded warts commonly found on the hands and fingers
- HPV-3 and HPV-7 cause flat, round warts that typically grow on the face and backs of the hands
- HPV-1, which causes plantar warts on the plantar surfaces, or soles, of the feet

Common warts typically do not cause symptoms other than their appearance, which people tend to find cosmetically displeasing. Numerous products and methods are available to remove them. Over time, most warts left on their own gradually recede and disappear as the IMMUNE SYSTEM dispenses with the virus that causes them. Plantar warts, because they are on the walking surface of the foot, often become painful. Plantar warts are also more commonly spread among people, typically via exposure in locker rooms and shower rooms where people walk barefoot.

Genital HPV Infection

Genital HPV INFECTION is the most common of the SEXUALLY TRANSMITTED DISEASES (STDS) in the United States, causing new infection in over 5 million people each year. More than 20 million people currently have HPV infections. More than 40 strains of HPV cause genital HPV infection. These strains are contagious among people and spread via sexual contact (vaginal intercourse, anal intercourse, and oral sex). Some strains produce no symptoms.

HPV-6 and HPV-11 produce fleshy growths, often called genital warts, at the sites where the virus enters the body. Commonly genital warts grow on the tip of the PENIS, on the VULVA and at the opening of the VAGINA, and around the ANUS. Genital warts may also grow within the vagina and on the CERVIX in women and on the SCROTUM in men. Genital HPV may infect the MOUTH and THROAT through oral sex, though this is much less common than genital infection.

Women may first learn they have genital HPV infection during a ROUTINE MEDICAL EXAMINATION when the health-care provider detects genital warts inside the vagina and on the cervix. The gynecologist may perform COLPOSCOPY, an examination of the interior vagina with a specialized microscope, for further diagnostic assessment and to remove tissue samples (biopsy). Genital warts turn white after a few minutes when dabbed with a mild acetic acid solution (vinegar), providing the doctor with a quick diagnostic assessment. Laboratory examination of tissue samples from the growths can confirm the diagnosis.

Because genital warts continue to grow, which both cultivates and sheds the virus, doctors recommend treatment to remove them. Treatment options include medications, cryosurgery (freezing), electrocautery (burning), and laser therapy. Genital warts tend to recur, however, as long as the HPV infection remains present in the body.

TOPICAL MEDICATIONS TO TREAT HPV GENITAL WARTS

bichloracetic acid (BCA)	5-fluorouracil cream
imiquimod cream	podofilox solution
podophyllin solution	trichloroacetic acid (TCA)

Most HPV strains that cause genital infection do not produce symptoms. Many of these asymptomatic infections are benign (harmless) and go away in two or three years. Other genital HPV infections cause molecular changes in the cells of tissues. The tissues most commonly affected are the walls of the vagina and the cervix. These changes, called DYSPLASIA, are detectable only through microscopic examination of cells such as the doctor collects for a routine PAP TEST. Though often dysplasia resolves over time without treatment, it may progress to cancer. Doctors generally treat dysplasia to remove the risk for such progression.

Genital HPV Infection and Cancer

In recent years researchers have discovered that nearly all primary cervical cancer tumors contain one or more of 13 strains of HPV. Further, primary cervical cancer rarely occurs in women who have never had HPV infection. Cancer experts now believe HPV infection is the cause of primary cervical cancer. HPV types 16, 18, 31, 33, 39, 45, 51, 52, 56, 58, 59, 68, and 69 are the causative strains; HPV-16 and HPV-18 together account for about 85 percent of cervical cancers. Though these strains of HPV cause cervical cancer, only a small percentage of women infected with them develop cervical cancer. Routine Pap tests are a woman's best defense against HPV infection leading to cervical cancer because the changes in cells takes place slowly over years. Detecting and treating cervical or vaginal dysplasia eliminates the risk for the cells to continue a transition to cancer.

Preventing HPV Infection

Because human papillomaviruses are so prevalent, avoiding infection is difficult. Minimizing touch with common warts and treating them while they are small reduces the risk for spreading them to other parts of the body. Wearing shower sandals in locker rooms and public showers reduces the risk for contracting HPV-1 infection, which causes plantar warts.

Because of the risk for infection with one of the HPV strains linked with cancer, prevention measures are particularly important for genital HPV infection. Using latex condoms during all sexual activity greatly reduces the likelihood of contact with genital warts as well as with infected tissues that do not show symptoms. Annual Pap tests are essential for sexually active women. Men and women who have multiple sex partners have increased risk for genital HPV infection.

In 2006 the US Food and Drug Adminstration (FDA) approved the first vaccine to prevent infection with HPV types 6, 11, 16, and 18 in women. Administered as three injectons over 6 months, the vaccine appears to be highly effective with minimal side effects. However, the vaccine does not benefit women who already have HPV infection. Health experts recommend women through age 26 receive the HPV vaccine and girls receive HPV vaccine at age 11 or 12.

See also CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN); CHLAMYDIA; GENITAL HERPES; GONORRHEA; HIV/AIDS; SEXUAL HEALTH; SEXUALLY TRANSMITTED DISEASE (STD) PREVENTION; SYPHILIS.

I

immunization The mechanism through which the body protects itself from subsequent INFECTION with the same PATHOGEN. Immunization may occur as a natural consequence of infection or through vaccination (also called inoculation). The IMMUNE SYSTEM creates unique antibodies, specialized proteins that attach to B-cell lymphocytes that circulate in the BLOOD and the LYMPH, in response to antigens present on the cell surfaces of the pathogen. The antibodies then respond to the presence of the ANTIGEN within the body, activating a rapid IMMUNE RESPONSE to contain and neutralize the pathogen before it establishes sufficiently to cause illness. A VACCINE contains a nonpathogenic preparation of an antigen to stimulate the same immune response without causing illness. Natural immunization is usually lifelong. Immunization acquired through vaccination may require a series of vaccinations or periodic booster vaccines to maintain adequate protection against infection.

See also ANTIBODY; ANTIBODY-MEDIATED IMMUNITY; B-CELL LYMPHOCYTE; CHILDHOOD DISEASES; LYMPHOCYTE; PREVENTIVE HEALTH CARE AND IMMUNIZATION.

incubation period The length of time between the exposure to a PATHOGEN and the appearance of symptoms or illness. Incubation periods vary from a few hours (illnesses such as CHOLERA and SHIGELLOSIS) to months (illnesses such as HEPATITIS C, TUBERCULOSIS, and AMEBIASIS). Some diseases, such as AIDS (acquired immunodeficiency syndrome) and HUMAN PAPILLOMAVIRUS (HPV), may have incubation periods of years. During the incubation period the pathogen replicates until its presence reaches a level that can overcome the immune system's efforts to contain it. Viral infections in particular may be contagious during the incubation period.

See also BACTERIA; FUNGUS; HIV/AIDS; INFECTION; PARASITE; VIRUS.

infection The invasion of the body by a PATHOGEN (microorganism capable of causing disease), sometimes called an infectious agent, that enters cells and attempts to reproduce or replicate itself. The pathogen may be a bacterium, FUNGUS (yeast or mold), VIRUS, PARASITE, or prion. Not all infections cause symptoms or illness, and some infections may be present in the body for an extended time before they cause disease. The length of time between the entrance of a pathogen into the body and the appearance of symptoms is the illness's INCUBATION PERIOD.

The IMMUNE SYSTEM detects and in some way contains most pathogens. INFLAMMATION and FEVER, for example, are ways in which the immune response creates an unfavorable environment for many pathogens. Though the common perception that symptoms such as fever and MUSCLE aches are the effects of the infection, they are often instead the immune system's methods for eliminating the pathogen before its presence can cause illness.

Sometimes an infection is able to evade the immune system's efforts to eliminate it, such as HIV (human immunodeficiency virus), the infection that ultimately results in AIDS (acquired immunodeficiency syndrome). HIV actually infects the cells of the immune system that would fight its presence, restructuring their functions so they are no longer effective.

See also ANTIBODY-MEDIATED IMMUNITY; BACTERIA; CELL-MEDIATED IMMUNITY; IMMUNIZATION.

influenza A common and potentially serious viral INFECTION, commonly called the flu, that

causes upper respiratory symptoms. Influenza viruses rapidly adapt and mutate, which gives them the perpetual ability to cause illness. There are three types of human influenza VIRUS—influenza A, influenza B, and influenza C. Influenza A viruses are primarily responsible for annual outbreaks of the flu, though influenza B viruses also cause illness.

Some strains of influenza A infect humans and some strains infect animals such as pigs (swine influenza virus) and poultry (avian influenza virus). Strains of influenza A that infect animals can sometimes mutate in ways that permit them to cross over to infect people, as happened in 1918 with the world's most severe influenza pandemic, known as the Spanish flu (because the first cases occurred in Spain), which researchers today believe mutated from a variety of swine influenza virus.

Symptoms and Diagnostic Path

Influenza is an illness of the upper respiratory tract, the symptoms of which tend to emerge rapidly and full-force. Symptoms of influenza include

- high FEVER (102°F or higher)
- severe HEADACHE
- muscle aches and JOINT PAIN
- nonproductive COUGH
- sore THROAT
- nasal and sinus congestion

Some people, especially young children, may experience NAUSEA and VOMITING. However, gastrointestinal symptoms are not characteristic of influenza, and their prominent presence suggests a different infection. There are several tests available for influenza, including rapid tests that the doctor can use in the office as well as blood tests.

Treatment Options and Outlook

Most often, the flu simply runs its course and treatment targets relieving symptoms such as fever and aches. Rest, fluids, and nutritious foods are important for helping the body to fight the virus. Secondary bacterial infections and other complications can occur and require appropriate treatment. ANTIBIOTIC MEDICATIONS are not effective for treating viruses, though the doctor may prescribe an antibiotic to treat a secondary bacterial infection that develops, such as PNEUMONIA or STREP THROAT. The most common complication of influenza is PNEUMOCOCCAL PNEUMONIA, a bacterial infection for which there is a one-time vaccine (though people who have lung disorders or respiratory compromise may need a second vaccine 10 years after the first vaccine).

The flu vaccine IMMUNIZATION remains the frontline of treatment for influenza. Each year researchers determine the two strains of influenza A and one strain of influenza B most likely to cause infection (based on complex algorithms of historic and projected viral cycles). Manufacturers then cultivate the three strains to create the year's VACCINE. This is a somewhat speculative approach, however, and the actual strains of influenza that surface may be entirely different. When the strains are similar to those in the vaccine the vaccine is highly effective in preventing or moderating influenza infection. When the strains are not at all close, the vaccine offers no protection from influenza infection. Because the influenza virus so rapidly mutates, each vaccine is effective only for a single flu season.

Antiviral medications ANTIVIRAL MEDICATIONS may shorten the course of illness and lessen the severity of symptoms when taken within 48 hours of the first symptoms and may prevent infection with influenza after exposure to someone who has the viral infection. Antiviral medications work by interfering with the mechanisms viruses use to alter the functions of their host cells, typically by blocking the action of key enzymes or proteins that the virus uses to instruct RNA to take over the host cell. Some antiviral medications are effective against influenza A (amantadine and rimantadine) and others against influenza B (zanamivir and oseltamivir). Further testament to the influenza virus's ability to mutate is the emergence of influenza virus strains that are resistant to amantadine and rimantadine.

Risk Factors and Preventive Measures

People at highest risk for influenza are the very young, the very old, and those who have compro-

mised immune function, such as people who have HIV/AIDS or CANCER or who take IMMUNOSUPPRESSIVE THERAPY after ORGAN TRANSPLANTATION. People who have DIABETES and other chronic health conditions also have increased risk for infection. Preventive measures to reduce the risk for influenza infection include

- frequent HAND WASHING with warm water and soap
- disinfecting common use surfaces such as doorknobs
- minimizing exposure to enclosed crowds of people during peak flu season (November through March in the United States)

Annual flu vaccines are currently the most effective method for preventing influenza.

See also BACTERIA; INFLUENZA PREVENTION; SNEEZE/COUGH ETIQUETTE.

L–M

listeriosis An illness that results from INFECTION with the bacterium *Listeria monocytogenes*. Listeriosis most often occurs as a foodborne illness and has the potential to cause serious symptoms. *L. monocytogenes* are normally present in soil and can contaminate milking equipment. Animals also can carry *L. monocytogenes* without illness. The most common sources of listeriosis are unpasteurized milk and cheeses and processed foods that become contaminated after processing, such as lunch meats served in delis and restaurants. Thorough cooking and pasteurization kill *L. monocytogenes* BACTERIA.

Symptoms and Diagnostic Path

Symptoms of listeriosis are often fairly severe and many people who develop the illness require hospitalization for treatment. Symptoms may include

- FEVER
- difficulty BREATHING (DYSPNEA)
- NAUSEA and VOMITING
- MUSCLE aches and JOINT PAIN

Symptoms may also be specific to the type of infection, such as MENINGITIS or PNEUMONIA. The diagnostic path includes BLOOD cultures and, when neurologic symptoms are present, LUMBAR PUNCTURE to examine and culture the spinal fluid. The presence of *L. monocytogenes* confirms the diagnosis.

Treatment Options and Outlook

Treatment is antibiotic therapy, intravenous when symptoms are serious and oral when symptoms are moderate. Ampicillin, erythromycin, and sulfamethoxazole/trimethoprim (SMZ-TMP) are the antibiotics most effective; the usual course of antibiotic therapy may be four to six weeks. Most people fully recover with appropriate ANTIBIOTIC MEDICATIONS.

Risk Factors and Preventive Measures

People most at risk for listeriosis are those who are IMMUNOCOMPROMISED, particularly people who have HIV/AIDS. Pregnant women are also more vulnerable to infection and can pass the infection to their unborn babies; researchers believe this is due to the changes that take place in a woman's body under the influence of the hormones of PREGNANCY. Some pregnant women can harbor *L. monocytogenes* bacteria without becoming ill, though pass the infection to their babies. Listeriosis can cause STILLBIRTH (fetal death) and serious neurologic problems in newborns after birth. Health experts caution pregnant women (and other people at increased risk for listeriosis) to eat lunch meats and hot dogs only that are thoroughly reheated, to eat only pasteurized cheeses, to drink only pasteurized milk, and to wash all vegetables and fruits before eating them including lettuce) as methods for reducing their exposure to *L. monocytogenes* infection.

See also FOODBORNE ILLNESSES; FOOD SAFETY; HORMONE; WATERBORNE ILLNESSES.

Lyme disease An illness that results from INFECTION with the bacterium *Borrelia burgdorferi* in North America and other *Borrelia* species in Europe. The bite of the *Ixodes scapularis* tick, common in wooded areas throughout the northern United States, spreads the infection. *B. burgdorferi* infection primarily causes flulike symptoms though may also affect the CENTRAL NERVOUS SYSTEM, cardiovascular system, and the joints.

Symptoms of Lyme disease begin 5 to 30 days after a tick bite, typically with a characteristic RASH

called erythema migrans. The rash starts at the site of the bite and looks somewhat like a bull's eye around the bite. The rash expands over five to seven days, becoming large and raised, and may burn or hurt. The rash may also spread to other parts of the body.

Other symptoms may include

- FEVER
- HEADACHE
- MUSCLE aches and JOINT PAIN
- LYMPHADENOPATHY (swollen LYMPH nodes)

Though these symptoms, including the rash, will go away without treatment, the infection remains in the body and extends its involvement. Untreated Lyme disease may cause

- NEUROPATHY (tingling and numbness in PERIPHERAL NERVES), ENCEPHALOPATHY (disturbances of BRAIN function), and MENINGITIS (INFLAMMATION of the membranes that surround the brain and SPINAL CORD)
- BELL'S PALSY (PARALYSIS of the facial muscles)
- arthritis (inflammation of the joints), particularly in the knees and hips
- PALPITATIONS, dizziness, and changes in BLOOD PRESSURE resulting from cardiovascular involvement

BLOOD tests confirm the diagnosis. Treatment with ANTIBIOTIC MEDICATIONS eliminates the infection. People who receive early diagnosis and treatment nearly always recover quickly and fully. When the infection has spread to multiple body systems, residual effects may continue for several months.

ANTIBIOTIC MEDICATIONS TO TREAT LYME DISEASE

amoxicillin	ampicillin
azithromycin	cefuroxime
doxycycline	

Tick precautions when hiking or camping in tick-infested areas are the most effective means of preventing Lyme disease. Such precautions include wearing long pants tucked into high boots or socks to prevent ticks from attaching to the lower legs, examining the entire body for ticks after activities of possible exposure, and immediately removing any attached ticks. Because early treatment can avert serious complications, anyone bitten by a tick who develops rash or flulike symptoms should receive a medical evaluation for the possibility of Lyme disease or for ANTIBIOTIC PROPHYLAXIS (preventive antibiotic therapy).

See also ROCKY MOUNTAIN SPOTTED FEVER.

malaria An illness that results from INFECTION with one of four *Plasmodium* parasites: *Plasmodium malariae, P. ovale, P. vivax,* and *P. falciparum*. Bites from the female *Anopheles* mosquito spread the infection from one person to another. Though malaria has not occurred naturally in the United States since the 1950s, travel to or immigration from regions of the world where malaria is endemic results in about 1300 cases of malaria in the United States each year.

Malaria can be serious or fatal without treatment and is a major cause of death worldwide, particularly in developing nations with limited access to medical resources. Malaria is particularly devastating in the Sahara and sub-Sahara regions of the African continent, where it claims the life of one child every 30 seconds. Extreme poverty, lack of medical resources, and environmental conditions in which mosquito populations flourish converge in these regions, maintaining an endemic presence of malaria that is the most extensive in the world.

Plasmodium parasites initially infect LIVER cells, where they reproduce. They then migrate into erythrocytes (red BLOOD cells), entering the blood circulation. The INCUBATION PERIOD ranges from 8 days to several months, after which flulike symptoms emerge that include

- FEVER and chills
- HEADACHE
- MUSCLE aches
- NAUSEA, VOMITING, and DIARRHEA
- JAUNDICE (yellow discoloration of the SKIN)
- tiredness or fatigue

Microscopic examination of a blood sample shows the parasites, confirming the diagnosis.

Early treatment with medications to kill the *Plasmodium* parasites is essential, particularly when the infective PARASITE is *P. falciparum,* which causes life-threatening illness. Because antimalarial medications are effective against the parasites in the blood, it is essential to continue treatment through several life cycles of the parasites to kill those emerging from the liver. Only one antimalarial medication, primaquine, can kill liver-based *Plasmodium*. The specific medications and length of treatment depend on the type of infection, region of the world where the person acquired the infection, and the person's age and other health circumstances.

MEDICATIONS TO TREAT MALARIA

atovaquone-proguanil	chloroquine
doxycycline	mefloquine
primaquine	quinine
sulfadoxine-pyrimethamine	

Aggressive mosquito-control measures are the most successful preventive approach. These measures include public health efforts to eradicate mosquito populations, such as through insecticide application and eliminating standing water that serves as mosquito breeding grounds, and personal prevention efforts, such as wearing clothing that protects against mosquito bites. People planning travel to regions where *Plasmodium* infection is possible should take prophylactic medications.

See also ERYTHROCYTE; TOXOPLASMOSIS; TYPHOID FEVER.

measles An illness resulting from INFECTION with the measles VIRUS. Once among the most common childhood diseases worldwide, measles (also called rubeola) now primarily exists in developing nations where it remains a leading cause of childhood blindness and death. Routine measles IMMUNIZATION, the standard of care since becoming available in the early 1960s, has eradicated measles from much of the industrialized world. In the United States children generally receive measles VACCINE through the combination MMR (measles-mumps-rubella) vaccine.

Measles is one of the most highly contagious infections and spreads through droplet contamination via airborne transmission (sneezing and coughing) as well as direct contact. The virus invades the lining of the THROAT and the LUNGS, where it replicates. The virus then uses the lymphatic system to enter the BLOOD circulation, after which prodrome symptoms emerge that include

- FEVER
- sensitivity to light (PHOTOPHOBIA)
- congestion of the nasal passages and profuse nasal discharge
- nonproductive COUGH

Within two days the characteristic measles RASH emerges. This red, itchy rash starts at the hairline on the scalp and spreads to cover the entire body, including the palms of the hands and soles of the feet. The course of illness runs about 10 days after the rash begins. The infection is most contagious during the prodrome stage, though contagiousness continues through the rash stage. Diagnosis is clinical based on the characteristic nature of symptoms and history of exposure.

The risk for complications from measles is high, primarily because the measles virus's use of the IMMUNE SYSTEM to distribute itself compromises the IMMUNE RESPONSE, lowering resistance to infection from other pathogens. As a consequence secondary bacterial infections, notably OTITIS media (middle EAR infection) and PNEUMONIA, are common. Such bacterial infections require treatment with ANTIBIOTIC MEDICATIONS, though antibiotics do not treat measles. The measles virus may also cause viral pneumonia and MENINGITIS. IMMUNOGLOBULIN may prevent or moderate illness in people exposed to measles. However, ANTIVIRAL MEDICATIONS are not effective. Complications are more common in people who have vitamin A deficiency, though doctors do not know whether vitamin A supplementation during illness with measles decreases this risk.

See also BACTERIA; CHICKENPOX; MUMPS; PATHOGEN; PREVENTIVE HEALTH CARE AND IMMUNIZATION; SNEEZE/COUGH ETIQUETTE; VITAMINS AND HEALTH.

meningitis INFLAMMATION of the MENINGES, the membranes that surround the BRAIN and SPINAL CORD. Meningitis may result from bacterial, viral, or fungal INFECTION. Viruses are the most common causes of meningitis and can be highly contagious.

Enteroviruses and *Haemophilus influenzae* type B (Hib) VIRUS are the common viral causes, though many viruses can cause meningitis. Bacterial meningitis may be life threatening and requires immediate treatment with intravenous ANTIBIOTIC MEDICATIONS. The contagiousness of bacterial meningitis depends on the BACTERIA.

Symptoms and Diagnostic Path

Symptoms of meningitis tend to be milder with viral meningitis. They may appear gradually and include

- FEVER
- severe HEADACHE
- NAUSEA and VOMITING
- sore or stiff neck, or inability to touch the chin to the shoulder or chest
- agitation and confusion
- inability to remain alert or awake

LUMBAR PUNCTURE, which may reveal elevated cerebrospinal pressure and evidence of infection such as white BLOOD cells or the presence of bacteria, is the definitive diagnostic procedure.

Treatment Options and Outlook

Bacterial meningitis requires immediate treatment with antibiotic medications. Viral meningitis is self-limiting and usually improves on its own as the illness runs its course. Supportive treatment for viral meningitis may include intravenous fluids to maintain adequate HYDRATION. Complications that may occur with meningitis regardless of the causative PATHOGEN include swelling of the brain tissue, seizures, and diminished CONSCIOUSNESS. With appropriate treatment many people recover fully; some people have residual complications such as cognitive dysfunction, VISION IMPAIRMENT, or HEARING LOSS.

Risk Factors and Preventive Measures

The primary risk for meningitis is infection with any virus that can involve the meninges. Meningitis sometimes occurs in clusters of cases in settings where people live in close contact, such as college dormitories. People who are IMMUNOCOMPROMISED have increased risk for meningitis and many other kinds of infections. The most effective prevention measures are those that reduce the risk for acquiring viral infections—frequent HAND WASHING and diligent PERSONAL HYGIENE—and early treatment for symptoms of bacterial meningitis.

See also COGNITIVE FUNCTION AND DYSFUNCTION; ENCEPHALITIS; FUNGUS; VIRUS.

microbe A living organism, also called a microorganism, that is too small to see with the unaided EYE. Most microbes are single-cell or simple multiple cell organisms. Common microbes include BACTERIA, fungi (yeasts and molds), viruses, PROTOZOA, and algae. Microbes are abundant in the natural environment as well as the environment of the human body. Many microbes can cause INFECTION and illness in humans. Dutch scientist Antonie van Leeuwenhoek (1632–1723) identified many microbes using microscopes he constructed himself, paving the way for what would become the foundation of understanding for many disease processes.

See also FUNGUS; VIRUS.

mononucleosis, infectious An illness that results from INFECTION with the EPSTEIN-BARR VIRUS. Infectious mononucleosis is most prevalent among adolescents and young adults though may occur at any age. The infection spreads through contact with saliva; among young people and within families, sharing drinks and food are common means of contracting the illness. The Epstein-Barr VIRUS infects B-cell lymphocytes, also called mononuclear (single nucleus) lymphocytes, which is what gives the illness its name.

Symptoms and Diagnostic Path

The symptoms of infectious mononucleosis are flulike and generally mild to moderate in severity. Many people do not realize they have the illness. Symptoms include

- low-grade FEVER
- HEADACHE
- sore THROAT (PHARYNGITIS)
- fatigue
- cervical and axillary LYMPHADENOPATHY (swollen LYMPH nodes in the neck and underarms)

- abdominal tenderness
- slight JAUNDICE (yellow discoloration of the SKIN)

The diagnostic path includes BLOOD tests; the presence of abnormal lymphocytes and antibodies for Epstein-Barr virus confirms the diagnosis. Some people have mild HEPATITIS (INFLAMMATION of the LIVER), which blood tests also confirm, and mild to moderate SPLENOMEGALY (enlarged SPLEEN), which the doctor can detect with palpation (by feeling the abdomen).

Treatment Options and Outlook

Treatment is supportive, with rest and plenty of fluids. The course of illness may run three to six weeks, during which time the person is contagious and can spread the infection to other people. Most people recover fully, though it may take several months to feel back to normal. Though infectious mononucleosis is generally a benign, self-limiting viral infection, the Epstein-Barr virus remains in the body for life and is linked to certain kinds of cancer (notably Burkitt's lymphoma). A person can have infectious mononucleosis only once; the body develops IMMUNITY with infection.

Risk Factors and Preventive Measures

The Epstein-Barr virus is ubiquitous in the world; avoiding infection is nearly impossible. Measures such as frequent HAND WASHING and appropriate SNEEZE/COUGH ETIQUETTE reduce the risk for passing the infection to others. Adequate rest during the active illness reduces the risk for complications.

See also ANTIBODY; ANTIBODY-MEDIATED IMMUNITY; B-CELL LYMPHOCYTE; LYMPHOCYTE.

mumps An illness resulting from the mumps VIRUS, which primarily infects the SALIVARY GLANDS and may also involve the PANCREAS, TESTICLES (men), OVARIES (women), and sometimes the KIDNEYS. The mumps virus may also invade the CENTRAL NERVOUS SYSTEM, causing NEURITIS and ENCEPHALITIS. Since the advent of the mumps VACCINE in the early 1980s, mumps infections have become uncommon in the United States and now tend to occur in adults who did not have the INFECTION as children. Infection with mumps confers lifelong IMMUNITY, as does vaccination.

The mumps virus is contagious through contact with saliva, either direct or via airborne droplets. After an INCUBATION PERIOD of 14 to 21 days, symptoms emerge that include

- painful swelling of the parotid salivary glands at the base of the EAR
- HEADACHE
- sore THROAT
- FEVER

Swollen testicles are common in boys and lower abdominal PAIN, reflecting ovarian swelling, is common in girls. The classic "eat a pickle" test for mumps has some merit in that eating sour foods greatly intensifies the pain. However, the doctor usually makes the diagnosis on the basis of the symptoms and history of exposure or lack of IMMUNIZATION. Treatment targets symptom relief. Most people recover fully. A small percentage of people, usually adults, who acquire mumps infection develop neurosensory HEARING LOSS that is usually temporary. Mumps infection in both testicles (bilateral testicular mumps) can cause sterility, though this is uncommon. Though mumps encephalitis and MENINGITIS are serious complications, they are seldom fatal and most people recover without long-term consequences.

See also CHICKENPOX; CHILDHOOD DISEASES; MEASLES.

N–O

necrotizing fasciitis A rare but serious bacterial INFECTION of the fascia, the layer of connective tissue that covers, separates, and connects the muscles and other musculoskeletal structures. In necrotizing fasciitis a combination of aerobic and anaerobic bacterial activity produces an abundance of nitrogen, hydrogen, and methane gases. These gases act to suppress the activity of white BLOOD cells that ordinarily would move in to fight the infection. Necrotizing fasciitis is most commonly an OPPORTUNISTIC INFECTION that develops in people who have DIABETES, HIV/AIDS, and other circumstances of immunocompromise.

Nearly always the infection arises at or near the site of a wound, either accidental (more common) or surgical. Symptoms include sudden, severe PAIN at the site along with redness and slight swelling. The person generally feels and looks well in the early stages of the infection, then suddenly becomes critically ill. The redness of the RASH becomes purple, and the SKIN is odd to the touch. Often there is loss of sensation (traumatic ANESTHESIA) in the area. Necrotizing fasciitis moves very rapidly along the fascia into the deep tissues; the farther into the body it goes, the faster its progression because the anaerobic conditions (lack of oxygen) support its growth. Diagnosis is difficult in the early stages but unmistakable in the later stages. Blood cultures and cultures of tissue samples from the innermost edges of the infection generally reveal the causative BACTERIA, which allows doctors to choose effective ANTIBIOTIC MEDICATIONS.

Treatment is multifocused and includes intravenous antibiotics, usually multiple drugs, to attack the various types of bacteria involved in the infection as well as surgery to expose the infection to air (which reduces the ability of anaerobic bacteria to flourish) and remove dead and infected tissue so only healthy tissue remains. The surgical wounds are often significantly larger than the surface appearance of the infection would suggest because so much of the infection is deep within the body. Multiple operations are often necessary. Treatment with hyperbaric oxygen speeds improvement in some people.

With early detection and aggressive treatment that keeps necrotizing fasciitis fairly localized, the likelihood for recovery is good. When infection is extensive and other health conditions exist that challenge the IMMUNE RESPONSE, about 20 percent of people survive necrotizing fasciitis. Because researchers do not understand the complexity of circumstances that allows necrotizing fasciitis to develop, there are no methods for preventing infection. People who have any degree of immunocompromise should carefully monitor any wounds and seek prompt medical care for those that do not seem to follow a normal path of HEALING.

See also ANTIBIOTIC RESISTANCE; BOTULISM; GANGRENE; IMMUNOCOMPROMISED.

normal flora The BACTERIA, fungi, and other microorganisms naturally present within the environment of the healthy body. Normal flora exist on the surface of the SKIN, within natural cavities such as the NOSE and MOUTH, in the gastrointestinal tract, and in the reproductive tract. These beneficial microbes participate in the body's IMMUNE RESPONSE, digestive functions, and reproductive functions, among others.

Normal flora microbes exist in a balance that prevents one type of MICROBE from overpowering another. Circumstances that change this balance may allow illness to develop. Antibiotic therapy targets bacteria, for example, though antibiotics

cannot distinguish between normal flora and pathogenic bacteria. So ANTIBIOTIC MEDICATIONS, particularly broad-spectrum antibiotics, kill bacteria in the gastrointestinal tract and the reproductive tract at the same time they kill pathogenic bacteria. The result may be DIARRHEA or yeast VAGINITIS.

See also FUNGUS; INFECTION.

nosocomial infections Illnesses that result from INFECTION acquired in a hospital, skilled nursing facility, or other health-care facility. The PATHOGEN is typically bacterial, viral, or fungal. Many pathogens that cause nosocomial infections are resistant to common methods of treatment. The most common causes of nosocomial infections are

- invasive procedures ranging from intravenous (IV) lines and urinary catheters to surgery
- environmental factors such as air-conditioning and heating systems that harbor and distribute pathogens
- poor hygiene practices by staff (inadequate HAND WASHING, improper disposal of contaminated items)
- inappropriate separation of patients (such as medical patients roomed with surgical patients)

The risk for acquiring a nosocomial infection correlates directly to the length of time the person remains in the hospital or care facility—the longer the stay, the greater the risk. About 2 million people acquire nosocomial infections in the United States each year. Prevention efforts include improved infection control procedures and education for hospital and care facility staff.

See also ANTIBIOTIC RESISTANCE; BACTERIA; FUNGUS; LEGIONNAIRES' DISEASE; OPPORTUNISTIC INFECTION; VIRUS.

opportunistic infection Illness that develops in a person who is IMMUNOCOMPROMISED as a result of exposure to an otherwise benign MICROBE or a PATHOGEN a healthy IMMUNE SYSTEM could contain or eradicate. Opportunistic infections commonly occur in people who have HIV/AIDS, are receiving IMMUNOSUPPRESSIVE THERAPY after ORGAN TRANSPLANTATION, or are undergoing certain kinds of treatment for cancer. The weakened state of the IMMUNE SYSTEM allows infections to take hold as well as makes fighting the INFECTION more difficult.

COMMON OPPORTUNISTIC INFECTIONS

CANDIDIASIS	CYTOMEGALOVIRUS (CMV) INFECTION
HERPES SIMPLEX infection	COCCIDIOIDOMYCOSIS
CRYPTOCOCCOSIS	*Pneumocystis carinii* PNEUMONIA
TOXOPLASMOSIS	TUBERCULOSIS

See also NOSOCOMIAL INFECTION.

P–R

parasite An organism that requires coexistence with another organism for its survival. The parasite typically draws nourishment and other needs from its host organism without contributing in return to the host's survival. Some parasites can survive away from their hosts for limited periods of time or defined portions of their life cycles. Some parasites are host-specific whereas others can adapt to various hosts.

Pathogenic parasites are those that cause INFECTION and disease. Common pathogenic parasites include flukes, worms, and PROTOZOA (amebas). They may infect the SKIN or migrate to internal organs such as the LUNGS, LIVER, or BRAIN, where they often form cysts. Treatment for parasitic infections and illnesses depends on the parasite and the illness.

People who travel to tropical regions or areas where community sanitation is substandard may acquire parasitic infections otherwise uncommon in their home regions. Many systemic parasitic infections cause gastrointestinal symptoms such as DIARRHEA. These infections are usually contagious, spread through fecal–oral contact (contact with surfaces and substances such as food or water that are contaminated with particles of feces). Diligent PERSONAL HYGIENE, especially HAND WASHING, and appropriate FOOD SAFETY practices are key preventive measures.

COMMON PARASITIC INFECTIONS

AMEBIASIS	BABESIOSIS
CRYPTOSPORIDIOSIS	CYCLOSPORIASIS
GIARDIASIS	MALARIA
microsporidiosis	PEDICULOSIS
SCABIES	TRICHOMONIASIS

See also BACTERIA; FUNGI; MICROBE; VIRUS.

pathogen A MICROBE capable of causing illness. The most common pathogens are BACTERIA, fungi, parasites, and viruses. The process through which a pathogen, also called an infectious agent, causes illness is pathogenesis. The body attempts to protect itself from pathogens through numerous mechanisms, key among them being ANTIBODY-MEDIATED IMMUNITY and CELL-MEDIATED IMMUNITY. Vaccines and treatments with ANTIBIOTIC MEDICATIONS, ANTIVIRAL MEDICATIONS, and ANTIFUNGAL MEDICATIONS are among the methods available to contain and eradicate pathogens once they establish infection in the body.

See also FUNGUS; PARASITE; PROTOZOA; VACCINE; VIRUS.

pertussis An illness resulting from INFECTION with the VIRUS *Bordetella pertussis*. Pertussis is among the childhood diseases for which routine IMMUNIZATION is the standard of care in the United States. The hallmark of the illness is a rapid, violent cough that causes the person to make a "whooping" sound when trying to breathe through the coughing, hence the common term whooping cough. The cough can be severe enough to prevent BREATHING. Pertussis was once a leading cause of death among children under age 5. Though immunization has dramatically reduced infection, pertussis may still be fatal in very young children and very old adults. IMMUNITY, either natural (following infection and illness) or via VACCINE, lasts about 12 years.

The unmistakable cough is the primary symptom and begins about seven days after exposure. In untreated pertussis, the cough worsens rapidly and may continue for as long as eight weeks. Many people also experience VOMITING with the coughing. The doctor often makes the diagnosis on the basis

of the cough, though cultures taken from the MOUTH and NOSE may provide confirmation. Cultures are positive in about 80 percent of people.

Treatment in the early stages of pertussis is ANTIBIOTIC MEDICATIONS, typically erythromycin or trimethoprim and sulfamethoxazole (TMP-SMZ). The further into the course of illness, the less effective antibiotics become, however. The infection causes the nasal passages, THROAT, bronchi, and bronchioles to ooze fluid that clogs the airways; the cough is the body's attempt to remove the fluid to permit free breathing. A profusely runny nose (rhinorrhea) is the earliest symptom of pertussis though often is perceived as a cold until the cough begins. Antibiotic therapy can substantially shorten the course and lessen the severity of illness. Most people recover fully with appropriate treatment, particularly when treatment begins early.

See also CHILDHOOD DISEASES; DIPHTHERIA; PREVENTIVE HEALTH CARE AND IMMUNIZATION.

pneumococcal pneumonia An illness resulting from INFECTION with the bacterium *Streptococcus pneumoniae*, which is normally present in the mucous membranes of the NOSE and sinuses. Researchers do not know what processes occur in the body that allow *S. pneumoniae* to shift from NORMAL FLORA to causing infection in its native environment. Pneumococcal pneumonia is a serious upper respiratory illness that can invade the LUNGS and spread to the BRAIN (causing MENINGITIS) and middle EAR (causing OTITIS media). Pneumococcal pneumonia can also cause SEPTICEMIA, a life-threatening illness of widespread bacterial infection that involves multiple organ systems.

Symptoms and Diagnostic Path

Symptoms begin suddenly and are usually severe. They include

- a shaking chill followed immediately by sudden high FEVER
- nonproductive COUGH
- difficulty BREATHING (DYSPNEA) and CHEST PAIN
- HEADACHE
- NAUSEA and VOMITING
- fatigue

The diagnostic path includes chest X-RAY and BLOOD or fluid tests to determine the presence of *S. pneumoniae*. Because symptoms are severe and the risk for complications is high, doctors typically begin immediate treatment with ANTIBIOTIC MEDICATIONS. Symptoms that dramatically improve with the first 24 hours of treatment further confirm the diagnosis.

Treatment Options and Outlook

Penicillin is the antibiotic of first choice for treatment, though about 25 percent of *S. pneumococcal* strains are now resistant to it. Most resistant strains are sensitive to other antibiotic medications. The antibiotic of last resort is vancomycin, which doctors reserve for pneumonia that does not respond to treatment with any other antibiotics. With appropriate antibiotic therapy many people fully recover from pneumococcal pneumonia, though it is important to take the full course of antibiotics even after symptoms are gone. Pneumococcal pneumonia can be fatal.

ANTIBIOTIC MEDICATIONS TO TREAT PNEUMOCOCCAL PNEUMONIA

cefotaxime	ceftizoxime
ceftriaxone	clindamycin
erythromycin	gatifloxacin
grepafloxacin	levofloxacin
penicillin	moxifloxacin
sparfloxacin	vancomycin

Risk Factors and Preventive Measures

People most vulnerable to pneumococcal pneumonia are the very young, the very old, and those who are IMMUNOCOMPROMISED. The pneumococcal VACCINE, administered each year, can prevent *S. pneumoniae* infection.

See also ANTIBIOTIC RESISTANCE; INFLUENZA; INFLUENZA PREVENTION.

prion A protein fragment that becomes a PATHOGEN. Prion illnesses affect the BRAIN and cause extensive damage to brain tissue, causing it to become spongy in appearance. Though prion illnesses are not contagious in typical fashion, introduction of infectious prions into healthy brain tissue transmits the INFECTION. Because of these characteristics, researchers call prion illnesses

transmittable spongiform encephalopathies (TSEs). Some prion diseases are inherited and others are acquired. The most notorious prion illness is variant Creutzfeldt-Jakob disease (vCJD), acquired through the consumption of beef from cattle that have bovine spongiform encephalopathy (BSE), commonly called mad cow disease. Prions are highly resistant to disinfectants and sterilization procedures. Many hospitals now use disposable instruments for brain surgery to reduce the risk for transmitting a prion disease through an OPERATION.

See also CREUTZFELDT-JAKOB DISEASE (CJD); FOOD SAFETY.

prodrome The stage of illness immediately before the emergence of full symptoms. Prodrome is particularly prominent in herpesvirus INFECTION, which features tingling and irritation at the sites where herpes blisters are about to erupt. Prodrome occurs with many viral infections, such as MEASLES and CHICKENPOX. Often these infections are most contagious during the prodrome.

See also BLISTER; HERPES SIMPLEX; HERPES ZOSTER; GENITAL HERPES.

protozoa Single-celled organisms such as amebas. Many protozoa are parasitic and require host organisms for survival. Some protozoa are pathogenic, notably those that cause MALARIA and infections such as AMEBIASIS, BABESIOSIS, and GIARDIASIS. Some protozoal infections are self-limiting and others require treatment with medications such as antibiotics.

See also ANTIBIOTIC MEDICATIONS; BACTERIA; FUNGUS; PARASITE; VIRUS.

rabies A potentially fatal illness resulting from INFECTION with the rabies VIRUS, which belongs to the *Lyssavirus* viral family. Rabies is very rare in people though a common infection in wild animals who can transmit the infection to unvaccinated pets such as dogs and cats or to people through bites. Raccoons, skunks, coyotes, and bats are reservoirs for the rabies virus; though infected with the rabies virus, these animals do not themselves become ill with rabies. Nearly any animal may acquire rabies infection as a result of contact with saliva or other secretions from an infected animal, usually a bite.

In animals and humans the rabies virus infects the CENTRAL NERVOUS SYSTEM. It travels via the PERIPHERAL NERVES to the BRAIN, where it replicates within brain neurons (NERVE cells). Symptoms of illness generally appear one to three months after exposure, though the INCUBATION PERIOD may be as short as a few days or as long as several years. Once symptoms appear rabies is fatal. The illness of rabies is ENCEPHALITIS.

The most effective treatment for rabies infection in people is postexposure prophylaxis, which consists of one injection of human rabies IMMUNOGLOBULIN and five injections of rabies VACCINE administered at regular intervals after a bite from a potentially infected animal. The vaccine injections are given in the upper arm and are similar in discomfort to receiving a tetanus shot. The course of postexposure prophylaxis covers 28 days and appears to be 100 percent effective. People at high risk for rabies exposure, such as those who work with animals, can receive rabies vaccinations to prevent infection, though they also need postexposure prophylaxis if bitten.

See also IMMUNIZATION.

retroviruses See VIRUS.

Rocky Mountain spotted fever An illness resulting from INFECTION with the bacterium *Rickettsia rickettsii*. Tick bites spread Rocky Mountain spotted FEVER, so-named because of the characteristic RASH the illness causes. Symptoms generally appear within five days of a tick bite and include

- fever
- slight RASH
- NAUSEA and VOMITING
- severe HEADACHE
- MUSCLE PAIN

Symptoms become rapidly more severe as the illness progresses. Diagnosis is primarily clinical, based on the presentation of symptoms in combination with a history of tick bite or exposure to settings where tick bites are possible (such as hiking or camping in wooded areas). Treatment is prompt administration of doxycycline or tetracycline, ANTIBIOTIC MEDICATIONS that are especially

effective against *R. rickettsii*. Rapid improvement of symptoms confirms the diagnosis before BLOOD tests are able to do the same.

Most people fully recover with appropriate antibiotic treatment. However, Rocky Mountain spotted fever is life threatening for people who have G6PD DEFICIENCY, an inherited condition in which there is a lack of an enzyme important for maintaining red blood cells (erythrocytes). Age extremes (very young or very old) and chronic ALCOHOLISM are other factors that increase the severity of illness. Delayed treatment of Rocky Mountain spotted fever often results in multiple organ failure, requiring intensive medical treatment and a long recovery.

See also BACTERIA; ERYTHROCYTE; GENETIC DISORDERS; HUMAN EHRLICHIOSIS.

rubella An illness resulting from INFECTION with the rubella virus, a member of the *Rubivirus* viral family. Rubella, also called three-day MEASLES or German measles (because German researchers were the first to identify rubella as an illness separate from measles), is a mild course of illness in most people. However, the infection can cause serious BIRTH DEFECTS, collectively called congenital rubella syndrome, in a developing FETUS when a pregnant woman becomes infected during the first trimester of PREGNANCY.

Rubella is fairly contagious and spreads primarily through droplet inhalation (airborne transmission). The INCUBATION PERIOD is 14 to 21 days, after which most people experience low-grade FEVER; LYMPHADENOPATHY (swollen LYMPH nodes); and a red, slightly bumpy RASH that begins on the face and spreads to cover the entire body. Adults who get rubella often have PAIN and inflammation in the joints that continues for up to six weeks after other symptoms abate. Infection conveys lifelong IMMUNITY.

Rubella is among the diseases for which children in the United States receive routine IMMUNIZATION. This is particularly important because of the risk rubella infection presents to the unborn fetus. Congenital rubella syndrome affects about 90 percent of babies born to women who contract rubella during the first trimester of pregnancy. The syndrome's key features are

- HEARING LOSS, often profound (deafness)
- cataracts, GLAUCOMA, and RETINOPATHY
- pulmonary artery stenosis, ventral septal defect (VSD), patent ductus arteriosus (PDA), and other HEART anomalies
- impaired immune function
- early childhood development of type 1 DIABETES

Congenital rubella syndrome often causes lifelong health problems for affected children.

See also CATARACT; CATARACT EXTRACTION AND LENS REPLACEMENT; CHILDHOOD DISEASES; CONGENITAL HEART DISEASE; MEASLES; MUMPS; PREVENTIVE HEALTH CARE AND IMMUNIZATIONS; SCARLET FEVER.

S

salmonellosis An illness resulting from INFECTION with any of the numerous strains of *Salmonella* BACTERIA. *Salmonella* are common in the feces of birds and animals. Salmonellosis is most often a foodborne illness acquired through eating raw eggs, unpasteurized dairy products, and undercooked poultry. Reptiles kept as pets, such as turtles and iguanas, also carry *Salmonella*. Once salmonellosis develops, the infected person can spread it to other people.

The INCUBATION PERIOD (time between exposure and illness) is often less than 12 hours. The most common symptom of salmonellosis is DIARRHEA, which may be bloody or profuse. Other symptoms include abdominal discomfort, NAUSEA, VOMITING, and FEVER. The course of illness is self-limiting and runs four to seven days in otherwise healthy people. In people who are IMMUNOCOMPROMISED salmonellosis may occur as an OPPORTUNISTIC INFECTION that causes significant illness. Because salmonellosis is self-limiting, doctors do not usually prescribe ANTIBIOTIC MEDICATIONS to treat it even though the cause is bacterial. Researchers have discovered that the *Salmonella* bacteria remain longer in the bodies of people who receive antibiotics for salmonellosis, extending the possibility of spreading the infection to other people.

The most effective approach is prevention through proper food handling and diligent PERSONAL HYGIENE. Thorough cooking kills *Salmonella*. FOOD SAFETY procedures include

- washing the hands with soap and warm water before and after handling food
- thoroughly rinsing fresh fruits and vegetables in running water before eating or preparing them for meals
- using separate food preparation surfaces, such as cutting boards, and utensils for poultry and meats
- thoroughly cooking eggs, poultry, and other animal-based foods

See also FOODBORNE ILLNESSES; WATERBORNE ILLNESSES.

scarlet fever An illness resulting from INFECTION with group A beta-hemolytic streptococcal BACTERIA that occurs as a complication of STREP THROAT. Scarlet FEVER begins with the same symptoms as strep THROAT—sudden onset of fever and often severe throat PAIN. Within two days a RASH erupts, starting on the chest and back and spreading to cover the entire body. The key characteristic of the rash is that it feels like sandpaper to the touch. Other symptoms of scarlet fever include

- bright red, inflamed ("strawberry") tongue
- bright red color to the natural creases in the SKIN (under the arms and in the groin)
- HEADACHE
- peeling of the skin on the fingertips, on the tips of the toes, and in the creases of the groin

Scarlet fever, like strep throat, is contagious and spreads among people through airborne transmission or direct contact with saliva (such as through shared food or eating utensils). The diagnostic path includes culture of the throat to detect the presence of group A strep bacteria, though the symptoms are so characteristic the doctor can usually make the diagnosis on the basis of their presence (clinical diagnosis).

Treatment is with ANTIBIOTIC MEDICATIONS, typically penicillins or erythromycin. Most people rapidly and fully recover with appropriate antibiotic therapy. Though the infection may resolve without treatment, the risk is very high for the strep bacteria to migrate to other locations in the body, notably the HEART valves where it causes RHEUMATIC HEART DISEASE. The infection may also spread to the joints, causing INFECTIOUS ARTHRITIS.

See also PHARYNGITIS; SNEEZE/COUGH ETIQUETTE; TONSILLITIS.

septicemia A life-threatening bacterial INFECTION that invades the BLOOD circulation, resulting in spreading the infection throughout the body. Septicemia, also called bacteremia, typically arises as a complication of localized bacterial infection. The onset and progression of septicemia are rapid and can result in septic SHOCK, ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS), and death within hours. Treatment requires hospitalization, usually in an intensive care unit, with administration of intravenous ANTIBIOTIC MEDICATIONS as well as other medications to sustain vital functions such as HEART RATE and BLOOD PRESSURE. People who recover from septicemia tend to have a long path of recuperation before they are able to return to regular activities.

See also DISSEMINATED INTRAVASCULAR COAGULOPATHY (DIC); NECROTIZING FASCIITIS; TOXIC EPIDERMAL NECROLYSIS; TOXIC MEGACOLON; TOXIC SHOCK SYNDROME.

severe acute respiratory syndrome (SARS) A life-threatening illness resulting from INFECTION with the VIRUS SARS-associated coronavirus (SARS-CoV). The first outbreak of SARS occurred in 2003 and sickened more than 8,000 people in Asia, Europe, and South America. The handful of people infected in the United States acquired SARS during travel to countries experiencing outbreaks.

Infection occurs through close contact; SARS-CoV spreads through airborne droplets as well as direct touch with saliva and other bodily secretions that shed the virus. Symptoms appear 2 to 10 days after infection and begin with HEADACHE, general MUSCLE aches and JOINT PAIN, sore THROAT, and moderate FEVER. Within a few days shortness of breath (DYSPNEA) develops and may result in HYPOXIA (insufficient oxygen entering the BLOOD circulation for distribution to organs and tissues. Blood tests confirm the presence of SARS-CoV.

Treatment is primarily supportive; ANTIVIRAL MEDICATIONS may lessen the severity of symptoms. Some people require hospitalization in an intensive care unit with MECHANICAL VENTILATION and other medical care to support respiration and other vital functions while the illness runs its course. PNEUMONIA is the most common complication. The course of illness may run several weeks. Most people recover, though may require several months of recuperation before feeling well enough to return to their normal activities.

See also INCUBATION PERIOD.

shigellosis An illness resulting from INFECTION with any of numerous strains of *Shigella* BACTERIA. Shigellosis most commonly occurs as a foodborne illness, producing symptoms of FEVER, abdominal cramping, and bloody DIARRHEA within about 12 hours of infection with the bacteria. The illness is generally self-limiting, running its course in five to seven days. Most people recover fully, though for a small percentage the bacteria infect other areas of the body such as the joints, causing the chronic condition REITER'S SYNDROME.

Doctors may prescribe ANTIBIOTIC MEDICATIONS for the very young, the very old, and people who are IMMUNOCOMPROMISED or who have unusually severe and extended symptoms. Ampicillin, trimethoprim/sulfamethoxazole (TMP-STZ) combination, and ciprofloxacin are among the antibiotics doctors more commonly prescribe. Diligent PERSONAL HYGIENE and frequent HAND WASHING are the most effective means to curtail the spread of shigellosis from one person to another.

See also ANTIBIOTIC RESISTANCE; FOODBORNE ILLNESSES; FOOD SAFETY; WATERBORNE ILLNESSES.

smallpox An illness resulting from INFECTION with the *Variola* VIRUS. Though smallpox was once a much-feared and leading cause of death worldwide, aggressive vaccination efforts resulted in the World Health Organization's determination of its eradication as a naturally occurring disease in

1980. The last smallpox infection to occur in the United States was in 1949; the last smallpox infection in the world was in 1977 (Somalia).

The name derives from the characteristic appearance of small sores that BLISTER and then crust, or pox, on the body when illness emerges. The sores, along with FEVER, are the primary symptom. They are also the means by which the virus sheds; contact with the sores or the fluids they contain spreads the virus and the infection. Throughout history until its eradication in the 20th century, smallpox claimed the lives of a third of those infected and often left disfiguring scars on those who survived.

Because the risk for complications is relatively high with the smallpox VACCINE and there are no smallpox infections worldwide, routine vaccination for smallpox no longer occurs. Smallpox reemerged as a potential public health concern in the early 2000s with worries that it, along with other infectious pathogens such as ANTHRAX, could be used as a biologic weapon or bioterrorism agent. Governments around the world have prepared emergency response plans to cope with such potential actions. Though when smallpox occurred naturally as a disease there were no known treatments, researchers believe modern ANTIVIRAL MEDICATIONS would be effective against smallpox infection today.

See also IMMUNIZATION; PATHOGEN.

sneeze/cough etiquette A method of PERSONAL HYGIENE to help prevent the spread of INFECTION. Sneezing and coughing are among the mechanisms the body uses to expel bacterial and viral particles in illnesses such as COLDS and INFLUENZA. However, these particles spread the infection to others who breathe them in with the air or touch surfaces on which they land. Health experts recommend these procedures to reduce the risk of spreading infection through sneezing and coughing:

- SNEEZE or COUGH into a tissue that covers the NOSE and MOUTH, then discard the tissue and wash the hands with soap and warm water.
- Sneeze or cough into the crook of the arm, which is less likely to be a point of contact with surfaces and other people.
- Avoid shaking hands with other people during illnesses that cause sneezing or coughing.

See also BACTERIA; VIRUS.

strep throat An INFECTION of the pharynx (throat), also called streptococcal PHARYNGITIS, with various strains of group A beta-hemolytic streptococcal BACTERIA. Strep throat is highly contagious through contact with saliva and requires treatment with ANTIBIOTIC MEDICATIONS to prevent potentially serious complications such as RHEUMATIC HEART DISEASE.

Symptoms and Diagnostic Path

The symptoms of strep throat come on suddenly, usually within five days of exposure to the infection. A characteristic indication of strep throat is the appearance of symptoms without other cold-like symptoms. Only about 5 percent of sore throats (pharyngitis) are strep throat; most sore throats are viral infections. Key symptoms of strep throat include

- FEVER
- moderate to severe throat PAIN
- difficulty swallowing
- HEADACHE
- ABDOMINAL PAIN and VOMITING
- enlarged, painful LYMPH nodes in the neck
- MUSCLE aches and JOINT pain

Symptoms generally peak 48 hours after they first appear. The throat looks very red and may have pockets of pus (white patches or streaks), particularly on the tonsils. However, the throat's appearance is not diagnostically conclusive. A rapid ANTIGEN test, which produces results in minutes from a swab of the throat, is fairly accurate when positive but inaccurate when negative. A culture of the throat provides definitive diagnosis.

Treatment Options and Outlook

Antibiotic medications are necessary to treat strep throat. Because antibiotics do not help viral infections of the throat and because antibiotic-resistant strains of strep are beginning to appear, doctors

tend to wait for the throat culture results before prescribing antibiotic medications unless the person has a history of strep throat.

ANTIBIOTIC MEDICATIONS TO TREAT STREP THROAT	
ampicillin	azithromycin
cefaclor	cefazolin
cefuroxime	cephalexin
clarithromycin	penicillin VK

Most people recover fully with appropriate antibiotic therapy, with symptoms dramatically improved within 48 hours of starting the antibiotic. It is important to take the full course of antibiotic therapy even when symptoms are gone to make sure the antibiotic completely eliminates the strep bacteria. Possible complications of strep throat, which are more likely to occur with delayed treatment or in untreated strep throat, are serious and include PERITONSILLAR ABSCESS, GLOMERULONEPHRITIS (strep infection involving the KIDNEYS), and rheumatic heart disease (strep infection involving the HEART valves).

Risk Factors and Preventive Measures

Strep throat is most common in children between the ages of 5 and 15, though people of any age may acquire the infection. People who have their tonsils have greater risk. Diligent PERSONAL HYGIENE; frequent HAND WASHING; and avoiding the sharing of drinks, foods, and eating utensils among family members or friends are measures that can reduce the risk for exposure to the strep bacteria.

See also ANTIBIOTIC RESISTANCE; MENINGITIS; SCARLET FEVER; TOXIC SHOCK SYNDROME.

syphilis A sexually transmitted disease (STD) that results from INFECTION with the bacterium *Treponema pallidum*. Syphilis spreads through vaginal intercourse, anal intercourse, and oral sex. It is not possible to acquire syphilis from objects such as toilet seats or in hot tubs. Syphilis is curable with appropriate antibiotic therapy. Untreated syphilis can cause widespread damage in the body. Congenital syphilis, which a pregnant woman who has syphilis can pass to her unborn child, can cause numerous abnormalities or STILLBIRTH.

Symptoms and Diagnostic Path

Untreated syphilis has four stages: primary, secondary, latent, and tertiary. Symptoms are specific to the stage of illness. Diagnosis typically occurs through BLOOD tests that confirm the presence of antibodies or examination of cell samples (such as from body fluids) under a microscope that reveal the presence of *T. pallidum* BACTERIA.

Primary syphilis Primary syphilis is the first manifestation of illness and occurs two to six weeks after infection with *T. pallidum*. Its symptom is the formation of a painless, ulcerlike sore (chancre) at the site where the infection entered the body. Because this site may be inside the VAGINA in a woman or within the URETHRA in a man, the chancre often goes undetected and heals.

Secondary syphilis Though the chancre heals the *T. pallidum* bacteria continue to multiply and invade the blood circulation, which carries them throughout the body. The characteristic symptoms of secondary syphilis emerge about two months after the chancre and include

- skin RASH of brown spots or sores that involves the palms of the hands and soles of the feet as well as other locations on the body
- mucous patches in the vagina or MOUTH and on the PENIS
- condylomata lata, which are spongy, wartlike patches that often appear on the labia (women) or SCROTUM (men)
- low-grade FEVER (around 100°F)
- sore THROAT and HEADACHE

Secondary syphilis lasts up to three months, during which the person can spread the infection to others through nonsexual as well as sexual contact because the sores of the rash contain *T. pallidum* bacteria. Some people experience outbreaks of secondary syphilis symptoms for a year or longer.

Latent syphilis In latent syphilis the bacteria remain in the body but cause no symptoms. During this stage the person cannot pass the infection to other people. Latent syphilis may last for decades, during which the bacteria silently attack the NERVOUS SYSTEM, joints, HEART, and other structures.

Tertiary syphilis The last stage of syphilis, the tertiary stage, is the emergence of symptoms resulting from the damage that occurred during the latent stage. Damage is often widespread and significant, producing symptoms of cognitive dysfunction, blindness, heart disease, kidney disease, and NEUROPATHY (sometimes called neurosyphilis).

Treatment Options and Outlook

Treatment for syphilis at any stage is penicillin by injection (or doxycycline for people who are allergic to penicillin). Most people who receive treatment for primary or secondary syphilis recover completely. Treatment can still cure tertiary syphilis but the damage the infection has already caused is permanent. Reinfection is possible; there is no IMMUNITY for syphilis. All sexual partners should be tested so they can receive treatment if they have syphilis. Primary syphilis carries increased risk for HIV infection because the chancre gives an easy pathway for the VIRUS to enter the body.

Risk Factors and Preventive Measures

People who have multiple sexual partners and men who have sex with men have the greatest risk for contracting syphilis and other STDs. Precautions such as condom use with all sexual activity reduce the risk for infection. Early diagnosis and treatment are essential to prevent complications and to prevent spreading the infection to other people.

See also CHLAMYDIA; GENITAL HERPES; GONORRHEA; HUMAN PAPILLOMAVIRUS (HPV); SEXUAL HEALTH; SEXUALLY TRANSMITTED DISEASE (STD) PREVENTION; SEXUALLY TRANSMITTED DISEASES (STDS).

T

toxic shock syndrome A systemic IMMUNE RESPONSE to the endotoxins many BACTERIA produce during infections. The immune response produces widespread, significant INFLAMMATION involving multiple organ systems. Staphylococcal toxic shock syndrome, resulting from *Staphylococcus aureus* INFECTION, is more common and causes milder illness. Streptococcal toxic shock syndrome, which results from group A beta-hemolytic streptococcal bacteria, produces severe illness and causes death in about 60 percent of people who develop it.

Symptoms are those of acute bacterial infection such as FEVER and PAIN, with HYPOTENSION (low BLOOD PRESSURE) and RASH that involves the entire body, including the palms of the hands and soles of the feet. Illness is severe enough to require hospitalization, often in an intensive care unit, for supportive medical care (including fluid replacement, cardiovascular stabilization, and MECHANICAL VENTILATION as necessary) and treatment with intravenous IMMUNOGLOBULIN and ANTIBIOTIC MEDICATIONS. Complications of toxic shock syndrome are potentially life-threatening and include DISSEMINATED INTRAVASCULAR COAGULATION (DIC), ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS), and NECROTIZING FASCIITIS. People who recover from toxic shock syndrome may have lingering health problems and are at risk for RECURRENCE.

Toxic shock syndrome first emerged as a significant health issue in the 1980s when superabsorbent tampons new on the market caused an outbreak of toxic shock syndrome among otherwise healthy women. The superabsorbency of the tampons meant women could change them less frequently, an unexpected SIDE EFFECT of which was a spike in bacterial infections. Changes in tampon materials and widespread education efforts have significantly reduced toxic shock syndrome due to tampon use, although tampon use remains a risk factor. Other risks for toxic shock syndrome include surgical packing (such as after an OPERATION on the NOSE) and illness due to common bacterial infections.

See also SCARLET FEVER; STREP THROAT; SEPTICEMIA.

toxoplasmosis An illness that results from INFECTION with the PARASITE *Toxoplasma gondii*. Health experts in the United States estimate that about 60 million Americans are infected with *T. gondii,* though only a small percentage of them become ill. *T. gondii* may migrate into body tissues, forming cysts.

Domestic cats carry *T. gondii*; cat feces in litter boxes and outdoors in garden areas are the most common source of infection. Outdoor cats are more likely to have *T. gondii*. Other sources of *T. gondii* include undercooked or raw meats, especially pork and lamb. People acquire the infection through touching contaminated objects and then transmitting the parasites to food or drink. Children may acquire *T. gondii* infection through playing in outdoor sandboxes.

Toxoplasmosis is often an OPPORTUNISTIC INFECTION that causes illness in people who are IMMUNOCOMPROMISED, such as people who have HIV/AIDS or who are taking IMMUNOSUPPRESSIVE THERAPY after ORGAN TRANSPLANTATION. Toxoplasmosis, whether or not it produces symptoms, is a particular risk for a pregnant woman because she can pass the infection to her unborn child. The cysts that *T. gondii* form in the tissues can cause serious BIRTH DEFECTS in the developing fetus, including damage to the eyes that results in permanent loss of vision. HEARING LOSS and neurologic injuries are also common.

Symptoms, when they occur, are similar to those of influenza and may include

- FEVER
- MUSCLE aches and JOINT PAIN
- upper respiratory congestion
- tiredness or fatigue

A BLOOD test that shows the presence of antibodies confirms the diagnosis. Anyone who has ever had toxoplasmosis will have a positive blood test; infection confers lifelong IMMUNITY. Toxoplasmosis is self-limiting; once the illness runs its course any symptoms subside. Though the *T. gondii* remain in the body, the IMMUNE SYSTEM can contain them so they do not cause illness. Doctors may recommend treatment with sulfadoxine and pyrimethamine, two medications used to prevent MALARIA, for pregnant women who acquire *T. gondii* infection or develop toxoplasmosis and for people who are immunocompromised. These medications are effective because *T. gondii* is similar to the parasite that causes malaria. The antibiotic clindamycin is also effective in people who are immunocompromised.

Washing the hands with warm water and soap after handling cats, cleaning litter boxes, gardening, and preparing pork or lamb removes *T. gondii*, preventing infection. Pregnant women should also wear gloves when gardening or cleaning litter boxes.

See also ANTIBIOTIC MEDICATIONS; HAND WASHING; INVESTIGATIONAL NEW DRUG (IND).

transmission modes The methods by which pathogens spread to cause INFECTION. Common transmission modes include

- airborne, in which pathogens enter the respiratory tract as particles suspended in the air
- sexual, in which pathogens enter the body through sexual contact
- direct contact, in which pathogens enter the body via touch
- foodborne, in which consumed foods contain pathogens
- waterborne, in which consumed water and foods prepared in that water contain pathogens
- bloodborne, in which pathogens enter the blood circulation through BLOOD TRANSFUSION or contaminated needles

Many infectious agents have multiple transmission modes. The common cold, for example, spreads through direct contact with nasal secretions as well as via airborne droplets.

See also COLDS; FOODBORNE ILLNESSES; PATHOGEN; SNEEZE/COUGH ETIQUETTE; WATERBORNE ILLNESSES.

trichomoniasis A sexually transmitted disease (STD) resulting from INFECTION with the protozoan *Trichomonas vaginalis*. Though trichomoniasis affects men and women equally, women are more likely to show symptoms. About two thirds of men and half of women who have trichomoniasis do not have symptoms, though they are nonetheless able to spread the infection through sexual contact.

Symptoms of trichomoniasis include

- greenish or yellowish, often foul-smelling, discharge
- lower abdominal discomfort
- in men, burning with URINATION
- in women, vaginal or vulvar itching or burning

The diagnostic path includes examination under the microscope of a sample of the discharge, which usually contains *T. vaginalis* though a third of people who have the infection may have negative findings with this test. Culture of discharge samples can provide definitive diagnosis. Treatment is oral therapy with the medication metronidazole. It is important to also treat all sexual partners, as the likelihood that they also have the infection is very high. Appropriate treatment cures trichomoniasis, though infection may recur with reexposure. Without treatment the infection remains active. Complications of untreated trichomoniasis include EPIDIDYMITIS and PROSTATITIS in men and chronic vaginitis and vaginal ulcerations in women.

See also CANDIDIASIS; CHLAMYDIA; GENITAL HERPES; GONORRHEA; HUMAN PAPILLOMAVIRUS (HPV); SEXUAL HEALTH; SEXUALLY TRANSMITTED DISEASE (STD) PREVENTION; SEXUALLY TRANSMITTED DISEASES (STDS); SYPHILIS; URETHRITIS.

tuberculosis An illness resulting from INFECTION with the MICROBE *Mycobacterium tuberculosis*. Though tuberculosis most commonly infects the LUNGS, the disease may involve other organs as well, notably the KIDNEYS. Health experts estimate more than 2 billion people worldwide have active (symptoms are present) or latent (symptoms are not present) tuberculosis. An important characteristic of mycobacteria is their ability to rapidly develop resistance to ANTIBIOTIC MEDICATIONS.

Untreated tuberculosis is debilitating and progressive, giving the appearance that it consumes the body. This characteristic accounts for the archaic common name of the disease, "consumption." Tuberculosis was a leading cause of death throughout the world until the discovery of the FUNGUS-derived antibiotic streptomycin in 1944. Today's treatment regimens seldom incorporate streptomycin, however, because of its high likelihood for causing HEARING LOSS (OTOTOXICITY) and because many strains of *M. tuberculosis* have developed resistance to it.

When breathed into the lungs, *M. tuberculosis* BACTERIA infect macrophages, white BLOOD cells responsible for consuming invading pathogens, in the alveoli. Rather than the MACROPHAGE consuming the *M. tuberculosis* bacterium, however, the bacterium takes over the macrophage. Other cells of the IMMUNE RESPONSE surround the infected macrophage, enclosing it within a GRANULOMA. The bacteria may remain dormant within the granuloma. When enough granulomas accumulate, they interfere with the normal function of the organ—typically the lungs, though also the kidneys, bones, and BRAIN when *M. tuberculosis* bacteria migrate to those structures.

Symptoms and Diagnostic Path

Many people who have tuberculosis do not have symptoms and do not know they have the infection. Chest X-RAY for other diagnostic reasons may detect lesions in the lungs; other people learn they have tuberculosis through routine tuberculin SKIN testing such as many states in the United States require for people who work with the public, such as health-care workers and food service workers. When symptoms are present they include

- prolonged, productive COUGH that may include blood (HEMOPTYSIS)
- unintended weight loss
- FEVER
- night sweats
- fatigue
- wheezing or feeling of tightness in chest

The diagnostic path includes chest X-ray, tuberculin skin test, and cultures of sputum samples. When the findings of these diagnostic procedures are inconclusive, the doctor may conduct additional tests, including BRONCHOSCOPY or COMPUTED TOMOGRAPHY (CT) SCAN.

Treatment Options and Outlook

Current treatment regimens use multiple medications in a rotating pattern over 9 to 12 months. The first phase of treatment—the initial phase, which lasts two months—generally involves taking four medications. The second phase of treatment—the continuation phase, which lasts four to seven months—generally incorporates a combination of two medications. The specific drugs depend on numerous clinical factors, including the person's HIV status and the sensitivities of the causative strain of *M. tuberculosis* from sputum cultures.

MEDICATIONS TO TREAT TUBERCULOSIS

Standard Infection	
ethambutol	isoniazid
pyrazinamid	rifabutin
rifampin	rifapentine
Resistant Infection	
amikacin	capreomycin
cycloserine	ethionamide
gatifloxacin	kanamycin
levofloxacin	moxifloxacin
p-aminosalicylic acid	protionamide
pyrazinamide	viomycin

Symptoms in most people improve dramatically within three weeks of starting medication, though clinical changes (X-ray) often do not become apparent for several months. Treatment regimens are complex, and the medications can cause unpleasant side effects, the combination of which tempts people to stop taking the medications.

Doing so is hazardous both for the person, who then remains infected with tuberculosis, and in the context of public health because it fosters DRUG resistance. It is essential to take the medications as directed for the full course of treatment. When compliance is a significant concern, doctors may use a protocol called directly observed treatment (DOT), in which the person comes to a clinic and takes his or her medication under direct observation of a health-care provider. Such treatment cures the tuberculosis. Any damage to the lungs or the kidneys (granulomas) remains, however, and is permanent.

Risk Factors and Preventive Measures

Crowded, unsanitary living conditions present the greatest risk for tuberculosis infection. Active tuberculosis is contagious through contact with sputum (material coughed up from the lungs), which contains *M. tuberculosis*. Latent tuberculosis is not contagious, though may emerge as active disease and become contagious. Tuberculosis is a common OPPORTUNISTIC INFECTION in people who have HIV/AIDS. Prevention efforts focus on routine testing of people at risk for exposure. In the United States, such testing takes place through public health programs, school-based programs, institutional programs (such as in the military and in prisons), and employer-based programs. People who have positive skin tuberculin tests should receive further evaluation from a doctor and may require a course of prophylactic treatment with anti-tuberculosis medications.

See also BONE; COMMUNITY SANITATION; PATHOGEN.

typhoid fever An illness resulting from INFECTION with the bacterium *Salmonella typhi*. Typhoid FEVER is rare in the United States, and most people who have the illness acquire the infection while traveling in regions of the world where typhoid fever is endemic. Substandard COMMUNITY SANITATION is the key risk for the spread of typhoid fever. The BACTERIA infect the SMALL INTESTINE. Infection spreads through fecal–oral contamination, primarily through consumption of contaminated water and foods. Some people are carriers of typhoid fever; they are infected with *S. typhi* but do not develop symptoms or illness.

Symptoms of typhoid fever include

- high fever
- NAUSEA, VOMITING, and DIARRHEA
- RASH
- ABDOMINAL PAIN
- extreme fatigue and weakness

Cultures of BLOOD and stool samples reveal the presence of *S. typhi*, which is conclusive for diagnosis. Treatment is ANTIBIOTIC MEDICATIONS, commonly ampicillin, trimethoprim-sulfamethoxazole (TMP-SMZ), or ciprofloxacin. Most people feel much improved within three days of starting antibiotic therapy, though the bacteria may remain in their bodies for six weeks or longer, during which time they remain contagious (capable of passing the infection to others). People who work in food service, health care, and other public contact jobs may require a doctor's statement of health, verifying negative blood and stool cultures, before they can return to work. People who are planning to travel to regions of the world where typhoid fever is common should receive typhoid fever VACCINE to prevent infection.

See also FOODBORNE ILLNESSES; WATERBORNE ILLNESSES.

V–W

virus An infectious PATHOGEN that must invade a host cell to replicate, technically called an obligate intracellular PARASITE. A virus is a particle of living material that contains an inner core of nucleic acid (DNA or RNA), called the genome, encased in an outer shell of protein, called a capsid. Some viruses contain a third layer composed of lipids, called an envelope, that further protects and nourishes the virus. These components, collectively called a virion, cannot themselves support a full life cycle, which obligates the virus to find a host to maintain its survival. A virus can attach only to the type of cell capable of supporting it, binding to specific protein molecules on the surface of the cell membrane.

ANTIBIOTIC MEDICATIONS are not effective in treating illnesses that result from viral infections, such as COLDS and INFLUENZA.

After invading a host cell, a virus hijacks the cell's structures and functions to serve its own needs and to replicate itself. DNA viruses produce

COMMON VIRUSES AND THE ILLNESSES THEY CAUSE

Virus or Viral Family	Genetic Configuration	Illness
ADENOVIRUS	DNA	PHARYNGITIS, PNEUMONIA, acute respiratory disease, cervicitis, URETHRITIS, CYSTITIS, GASTROENTERITIS
CYTOMEGALOVIRUS (CMV)	DNA	CMV INFECTION
EPSTEIN-BARR VIRUS	DNA	infectious mononucleosis, Burkitt's lymphoma, Hodgkin's lymphoma
HEPATITIS A virus (HAV), hepatitis C virus (HBV)	RNA	HEPATITIS
HERPES SIMPLEX virus 1 (HSV-1)	DNA	COLD SORE
herpes simplex virus 2 (HSV-2)	DNA	GENITAL HERPES
human herpesvirus 8 (HHV-8)	DNA	KAPOSI'S SARCOMA
human immunodeficiency virus 1 (HIV-1), human immunodeficiency virus 2 (HIV-2)	RNA retrovirus	AIDS

Virus or Viral Family	Genetic Configuration	Illness
human papillomavirus (HPV)	DNA	genital WARTS, CERVICAL CANCER, vaginal cancer
human parainfluenza viruses	RNA	acute upper respiratory disease, CROUP, bronchiolitis, BRONCHITIS, pneumonia
INFLUENZA viruses	RNA	influenza (flu)
MEASLES virus	RNA	measles
MUMPS virus	RNA	mumps
Norwalk-like viruses	RNA	acute gastroenteritis
poliovirus	RNA	POLIOMYELITIS
RABIES virus	RNA	rabies
respiratory syncytial virus	RNA	bronchiolitis, pneumonia, acute upper respiratory disease
rhinoviruses	RNA	COLDS
RUBELLA virus	RNA	rubella (German or three-day measles)
varicella-zoster	DNA	CHICKENPOX, HERPES ZOSTER (shingles)
variola	DNA	SMALLPOX

proteins that the host cell's RNA transcribe as instructions to replicate the virus's DNA, which the cell does. DNA contains the instructions for the cell's functions; RNA forms the messenger proteins that carry out the directives of the DNA. Eventually the virus's copies of DNA crowd out the cell's copies of DNA, and the cell becomes the agent of the virus. The cell either divides or ruptures, spreading the virus. RNA viruses achieve a similar result by causing the host cell to replicate their RNA, which then replaces the cell's RNA. Retroviruses are RNA viruses that contain the enzyme reverse transcriptase, which allows RNA to instruct DNA (the reverse of normal).

Viruses are highly adaptable and have numerous mechanisms to hide from the IMMUNE SYSTEM, allowing them to become well established infections before the immune system detects their presence. Once the immune system does detect a virus, it develops antibodies that protect against subsequent infection by the same virus. Many common viruses—such as those that are responsible for COLDS (rhinoviruses), GASTROENTERITIS (enteroviruses), and the flu (INFLUENZA viruses)—frequently alter their structures, evolving into different strains that can cause the same illnesses. Some viruses, such as human T-lymphotropic virus (HTLV) and HUMAN PAPILLOMAVIRUS (HPV), cause cancer (oncoviruses). The human immunodeficiency virus (HIV) is a retrovirus that attacks the immune system, causing AIDS (acquired immunodeficiency syndrome).

See also ANTIBODY; ANTIBODY-MEDIATED IMMUNITY; CELL-MEDIATED IMMUNITY; HIV/AIDS.

waterborne illnesses Diseases that result from pathogens transmitted by drinking or otherwise consuming contaminated water. Heavy metals and

industrial chemicals may also contaminate water supplies, causing poisoning. People may acquire waterborne infections through drinking water supplies or by swallowing water during recreational activities in lakes, rivers, pools, hot tubs, and similar sources.

Drinking water supplies in the United States must meet established DRINKING WATER STANDARDS for purity, which state and local health departments monitor through regular and spontaneous testing. Water that does not come from a community water supply or properly maintained and disinfected private well should be boiled for one minute, then cooled, before drinking or using to prepare food.

Environmental water sources such as lakes and rivers contain numerous BACTERIA and parasites that can cause illness with contact or consumption. Contamination is higher after steady or heavy rain, as runoff water that drains into streams, rivers, and lakes is likely to contain animal excrement as well as soil-based microbes. Recreational activities such as boating, swimming, water-skiing, and fishing hold increased risk for exposure to such pathogens. It is important to avoid swallowing environmental water and to shower to rinse the SKIN after being in the water. People who hike and camp in back-country areas should use appropriate decontamination or filtration methods to draw drinking water from natural sources. A rapidly moving stream or river does not necessarily contain fewer microbes, and the clearness of water's appearance does not mean it is safe to drink.

COMMON WATERBORNE ILLNESSES

CRYPTOSPORIDIOSIS	*Escherichia coli* INFECTION
GIARDIASIS	HEPATITIS A
AMEBIASIS	CYCLOSPORIASIS
CAMPYLOBACTERIOSIS	SALMONELLOSIS
SHIGELLOSIS	viral GASTROENTERITIS

See also COMMUNITY SANITATION; ENVIRONMENTAL HAZARD EXPOSURE; FOODBORNE ILLNESSES; FOOD SAFETY; HEAVY-METAL POISONING; HEPATITIS PREVENTION; PARASITE; POISON PREVENTION.

CANCER

The area of health care concerned with cancer prevention and treatment is oncology. Doctors who specialize in cancer treatment are oncologists. This section, "Cancer," presents an overview discussion of current understanding about cancer and entries about cancer concepts and treatments. Entries in other sections of The Facts On File Encyclopedia of Health and Medicine *provide detailed content about specific types of cancer.*

For example, this section, "Cancer," contains the entry HORMONE-DRIVEN CANCERS, whereas while the section "The Reproductive System" contains entries for BREAST CANCER, PROSTATE CANCER, and TESTICULAR CANCER. Cross-references connect entries with one another.

Cancer: Uncontrolled Cell Proliferation

Cancer is the uncontrolled growth and division (proliferation) of cells. Cancer cells lack the proper mechanisms for APOPTOSIS, the natural process that establishes the end of a cell's life cycle. In this regard, cancer cells have an endless open throttle: they can divide forever. Cancer cells also lack the proper mechanisms for self-regulation that shut down cell division in abnormal cells; they never stop growing and dividing.

Ordinarily the IMMUNE SYSTEM detects cells that present a threat to the body and mobilizes an IMMUNE RESPONSE to neutralize them before they can do much damage. Cancer cells appear able to evade such detection by the immune system because they arise from cells that belong to the body (self cells). Even as they mutate cancer cells retain enough essence of their self-cell origin to fool the immune system into continuing to perceive them as self cells. This deception allows cancer cells to congregate, forming the tumors that characterize the disease process of cancer.

Cancer may develop in any cell, with the potential to affect any kind of body tissue. The cells form tumors that invade healthy tissues and can spread to parts of the body beyond the site of origin. Cancer is a threat to health because its presence within tissues and organs disrupts their structure and functions. Cancer tumors take space, NUTRIENTS, and structure that tissues and organs need.

Heredity, Environment, and Aging

Researchers believe cancer is the result of genetic damage within individual cells that allows uncontrolled cell division and growth. This damage may occur as a consequence of heredity or environment or may develop through the process of aging.

Heredity and cancer The tendency toward cancer appears to run in families, providing much anecdotal evidence of genetic mutations that contribute to the risk for cancer. Researchers also have isolated specific genes for certain types of cancer, providing objective evidence that cancer can have a hereditary component. When this is the case, a person inherits mutated genes that do not properly regulate specific functions. This lack of regulation results in abnormal cell growth and division that can result in cancer. The BRCA-1/BRCA-2 GENE mutations are among the best known; these mutations are prominent in women who have some types of OVARIAN CANCER or breast cancer. However, only a small percentage of women who have these gene mutations develop cancer, evidence that many factors converge when cancer occurs.

Environmental influences and cancer More than a thousand substances found in the environment, natural and synthetic, may cause cancer.

Most are chemicals or sources of radiation, both of which alter the molecular structure of cells in ways that change their functions. The most common natural CARCINOGEN is the ultraviolet radiation of sunlight, which is responsible for nearly all SKIN CANCER. Other carcinogens are manmade, notably industrial chemicals such as formaldehyde and vinyl chloride. Many manufacturing processes use these and other carcinogenic chemicals; it is nearly impossible to avoid exposure to them.

Aging and cancer Genetic damage to cells may also occur as a consequence of natural deterioration within cells that takes place with aging. Cells become less able to repair themselves and exposure to carcinogens leaves them more vulnerable, allowing errant growth and division. Some cancers that are more common in advanced age are also less harmful to health overall. For example, researchers estimate that 90 percent of men over age 85 have prostate cancer, yet in most of them the cancer is so slow growing that it does not require treatment.

Traditions in Medical History

Surgery was the first treatment for cancer. Even ancient documents record procedures for removal of tumors. However, the development of ANESTHESIA gave surgery its big boost as treatment for cancer, allowing surgeons to more selectively remove cancerous tumors. Though the operations were often extensive and traumatic, they were able to save lives.

RADIATION THERAPY was the next treatment developed for cancer. Though doctors began using X-rays on tumors shortly after the discovery of X-rays in the late 19th century, the treatment was often more dangerous than the cancer. Radiation BURNS and radiation sickness were common as doctors struggled to find a balance between enough radiation to kill the tumor and not enough radiation to kill the patient. Finally, in the middle of the 20th century advances in technology and understanding made it possible for radiation to achieve this balance.

For centuries folk medicine contained various substances purported to treat cancer, some of which have become the basis for contemporary CHEMOTHERAPY (such as the camptothecins, vinca alkyloids, and taxanes). During the first half of the 20th century doctors realized that one SIDE EFFECT of poisonous mustard gas, used as a weapon of war, was that it eradicated certain types of cancer. Further exploration resulted in the first class of therapeutic chemotherapy agents, the alkylating agents.

In the later decades of the 20th century, researchers made significant breakthroughs in understanding the functions of the immune system and were able to develop methods to take advantage of the body's own mechanisms for fighting cancer. IMMUNOTHERAPY is now at the forefront of cancer research.

Breakthrough Research and Treatment Advances

Cancer treatment focuses on removing or disabling cancer cells so they can no longer grow and divide. Though cancer remains the second-leading cause of death in the United States, successes in treatments since the 1990s have improved the outlook significantly. Nearly 10 million Americans live with their cancer under control, in REMISSION, or cured. Treatment is so often curative for basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), the two most common types of SKIN cancer, that cancer statistics do not include these cancers among them.

As researchers learn more about cancer, they are discovering ways to bolster the immune system's ability to detect and eradicate cancer cells before they gain enough momentum to establish themselves as tumors. Cancer vaccines currently in investigational trials show great promise for preventing the development of CERVICAL CANCER, prostate cancer, and lymphoma, and for preventing the RECURRENCE of other types cancer. New treatments specifically target molecular functions, either in cancer cells or within the immune response. These therapies reduce the unpleasant side effects traditionally characteristic of cancer treatment as well as improve the ability to eradicate the cancer. Other therapies establish boundaries around the cancer, containing it so it cannot spread and interfere with structures and functions. Many types of cancer may soon be as manageable (and perhaps preventable) through therapeutic interventions and lifestyle modifications as other chronic health conditions such as CARDIOVASCULAR DISEASE (CVD) and DIABETES.

A–B

adenocarcinoma A type of cancer that arises from the endothelial cells of glandular structures. Adenocarcinoma is the most common type of cancer to occur in the PROSTATE GLAND (PROSTATE CANCER), gastrointestinal tract (ESOPHAGEAL CANCER, STOMACH CANCER, PANCREATIC CANCER, LIVER CANCER, COLORECTAL CANCER), and endocrine glands (TESTICULAR CANCER, OVARIAN CANCER, THYROID CANCER). Adenocarcinoma begins as a benign (noncancerous) tumor, an adenoma. Over time, GENE mutations in the cells of the adenoma may cause the tumor to transition to an adenocarcinoma. Adenocarcinomas can involve numerous organs and tissues.

See also BLASTOMA; CARCINOMA; ENDOCRINE GLAND; FAMILIAL ADENOMATOUS POLYPOSIS (FAP); HEREDITARY NONPOLYPOSIS COLORECTAL CANCER (HNPCC); INTESTINAL POLYP; LEUKEMIA; MUTATION; SARCOMA.

adenoma-to-carcinoma transition The changes that take place in an ADENOMA, a benign (noncancerous) tumor, as it transforms into an ADENOCARCINOMA, a malignant (cancerous) tumor. The transition to cancer can occur with any adenoma though is most common with adenomas of the colon (intestinal polyps, also called adenomatous polyps). Only a small percentage of adenomas become cancerous. The sequence of events that transform an adenoma to an adenocarcinoma begins with multiple mutations in the genes that regulate cell division and APOPTOSIS (planned cell death). Over a series of cell divisions the mutations become increasingly prevalent among the cells, resulting in DYSPLASIA and ultimately cancer. Because of the risk for an adenoma to become adenocarcinoma, doctors often surgically remove adenomas when feasible.

See also CANCER PREVENTION; COLORECTAL CANCER; FAMILIAL ADENOMATOUS POLYPOSIS (FAP); GENE; HEREDITARY NONPOLYPOSIS COLORECTAL CANCER (HNPCC); INTESTINAL POLYP; MUTATION.

adult survivors of childhood cancer The current generation of adults is the first to grow up in the era of successful treatment for many childhood cancers. Nearly 300,000 American adults who are now in their 20s, 30s, and 40s enjoy CANCER-free, healthy lives. Doctors consider treatments for most types of LEUKEMIA, the most common childhood cancer, to be curative. Treatments for many types of BONE CANCER, BRAIN cancer, Hodgkin's LYMPHOMA, and kidney cancer (WILMS'S TUMOR) are also curative. Some health concerns may linger or occur, however, as a result of the cancer itself or the therapies used to treat the cancer.

Complications of Cancer Treatment

Complications of cancer treatment are the most significant cause of later health concerns for adults who had cancer as children. Some therapies for cancer that were the standard of care 20 or 30 years ago presented significant health risks that survivors are now beginning to experience. For example, doctors now know the CHEMOTHERAPY drugs, notably anthracyclines such as doxorubicin, can cause HEART FAILURE that tends to show up 10 to 30 years after treatment. Chemotherapy drugs affect all rapidly dividing cells in the body and can have a significant effect on healthy cells notably in the endocrine system, affecting THYROID GLAND function, growth, PUBERTY, and FERTILITY. Radiation to the chest, such as to treat lymphoma, can damage the HEART, manifesting in adulthood as CARDIOMYOPATHY or heart failure. Radiation to the head

or EYE can result in vision and hearing problems. Surgery, particularly AMPUTATION, may result in lifelong health issues that require regular medical attention.

Increased Risk for Another Cancer

Having had cancer increases the risk for developing another cancer later in life. For this reason, regular health screening for cancer is especially important for adults who had cancer as children. Radiation therapy and chemotherapy both increase the risk for leukemia and lymphoma, likely as a consequence of damage to the bone marrow during cancer treatment and especially chemotherapy. Radiation therapy to the upper body raises the risk for lung cancer, particularly when other risk factors for lung cancer exist such as cigarette smoking, and for breast cancer in women.

Emotional Health

The emotional consequences of successful cancer treatment in childhood may be pervasive, with numerous effects people do not recognize as related to the cancer experience. Some studies show that adults who had cancer as children reexperience the range of emotions and fears that accompanied their cancer when as adults they enter medical environments for health care of any kind, often as a presentation of POST-TRAUMATIC STRESS DISORDER (PTSD). The reaction to the current situation may be out of proportion to the situation itself. Having survived a health crisis as serious as cancer as a child may have a profound effect on a person's ability to engage in activities of life, manifesting as withdrawal in some people and in high-risk behaviors in others.

Maintaining a Balanced Perspective

It is important for adults who had cancer as children to maintain a balance between diligence and confidence when it comes to health matters. More often than not, subsequent health concerns arising from childhood cancer or its treatment are treatable and manageable, particularly with early detection. Many cancer treatment centers now offer follow-up services, including counseling, for adult survivors of childhood cancer.

See also CANCER PREVENTION; CANCER RISK FACTORS; LIFESTYLE AND CANCER.

alternative and complementary remedies for cancer Therapies outside the realm of conventional medical methods that are promoted to relieve cancer symptoms. Alternative practices are used instead of conventional treatments and methods; complementary practices are used in conjunction with conventional treatments and methods. Some therapies and remedies may be either alternative or complementary, depending on how they are used. Because some cancer treatment protocols are very precise, it is important to discuss alternative and complementary approaches with the oncologist before using them.

Complementary Therapies

Complementary therapies are often effective for treating symptoms related to cancer and discomforts related to conventional cancer treatment. ACUPUNCTURE, BIOFEEDBACK, and HYPNOSIS can provide relief from PAIN and NAUSEA. YOGA, TAI CHI, and MEDITATION provide relaxation and stress relief. Some therapies, such as acupuncture and biofeedback, have undergone clinical research studies that support their effectiveness and usefulness. Most complementary therapies integrate well with conventional treatments. Some herbal remedies, such as products for nausea or relaxation, may interact with chemotherapy drugs.

Alternative Remedies

Alternative remedies for cancer are approaches to treat cancer that have not been proven effective through conventional research studies; some have been proven ineffective. Alternative therapies may include health-care systems that differ in philosophy and practice from conventional Western medicine, such as AYURVEDA, HOMEOPATHY, and TRADITIONAL CHINESE MEDICINE (TCM). Alternative remedies may also consist of conventional treatments used in unproven or disproven ways; most have either not been subjected to conventional research study or have been disproved. Some alternative remedies are potentially harmful in themselves as well as for the delay they may cause

in receiving conventional treatments that could have health benefits.

Making Choices and Decisions

Choices and decisions in regard to treatment for cancer are not easy to make, particularly when the diagnosis comes after the cancer is fairly advanced or has metastasized. Emotions are high, and sometimes the route of conventional treatment has little to offer beyond palliative care. Alternative remedies may make claims that sound too good to pass up. Cancer experts urge people to fully explore the remedy and the evidence that surrounds its usefulness. These key questions can help put the claims of the therapy or remedy in perspective:

- What does the remedy do—specifically? How does it affect the cancer?
- Does the remedy claim to be able to replace or support medical treatments?
- Who administers or provides the remedy?
- What are the remedy's possible side effects?
- What kinds of research have tested the remedy?
- What is the cost of the remedy?
- Is the remedy available in the United States?

Unfortunately, many purported cancer remedies are ineffective at best and potentially harmful. In some circumstances those who are marketing the remedy sincerely believe in its ability to treat or even cure cancer. However, the market for alternative remedies also offers abundant opportunity for fraud. Complementary therapies that supplement conventional treatment can provide comfort and relief from many symptoms related to cancer and cancer treatment. Choosing an ineffective alternative remedy in lieu of conventional treatment may have irreversible consequences for health and for QUALITY OF LIFE.

An oncologist or credentialed cancer care center can provide information and guidance for choosing complementary therapies that are helpful. The Web sites for the American Cancer Society (www.cancer.org), the US National Cancer Institute's Office of Cancer Complementary and Alternative Medicine (www.cancer.gov/cam), and the US National Center for Complementary and Alternative Medicine (nccam.nih.gov) provide current information about alternative remedies and complementary therapies for cancer.

See also CHEMOTHERAPY; COPING WITH CANCER; DIAGNOSING CANCER; RADIATION THERAPY; SURGERY FOR CANCER.

angiogenesis inhibitor drugs Substances that stop tumors from developing new BLOOD vessels to support their survival. Numerous proteins and enzymes in the body function to encourage or suppress the growth of new blood vessels. Cancerous tumors are among the tissues that produce proteins that foster new blood vessel growth; these blood vessels then deliver to the tumor the nourishment it needs to grow. Cutting off the blood supply starves the tumor, causing its cells to die.

Among the natural angiogenesis inhibitors in the body are the INTERFERONS, which doctors have used in therapeutic forms with some success to slow tumor-related blood vessel growth. Some CHEMOTHERAPY drugs also have a secondary antiangiogenesis effect. In 2004 the US Food and Drug Administration (FDA) approved the first DRUG specifically developed to block angiogenesis, a monoclonal antibody that is called bevacizumab (Avastin).

Angiogenesis inhibition is of therapeutic interest in health conditions other than cancer that result from overgrowth of blood vessels, such as AGE-RELATED MACULAR DEGENERATION (ARMD) and RETINOPATHY of DIABETES. Research into drugs to encourage angiogenesis to restore blood flow to the HEART after HEART ATTACK or in severe ISCHEMIC HEART DISEASE led to many advances in angiogenesis inhibition as well.

See also CELL STRUCTURE AND FUNCTION; MOLECULARLY TARGETED THERAPIES; MONOCLONAL ANTIBODIES (MABS); TRANSMYOCARDIAL LASER REVASCULARIZATION (TMLR).

blastoma A cancerous tumor that arises from the immature cells that form the basis for an organ's structure. The cells are undifferentiated, which means they have not yet developed a specific role within the body. Researchers believe these are embryonic cells. Blastomas grow as the

type of tissue where the embryonic cells remain after organ development. Blastomas nearly always occur in childhood, though occasionally may occur in early adulthood. Most blastomas are malignant (cancerous), though osteoblastoma (blastoma of the BONE) is a benign (noncancerous) tumor. Treatment for blastoma typically combines surgery to remove the tumor with CHEMOTHERAPY, RADIATION THERAPY, or both to shrink the tumor before surgery and destroy any lingering cancer cells after surgery. The precise combination depends on the tumor's location and size at the time of diagnosis.

TYPES OF BLASTOMA

Tumor	Location
medulloblastoma	BRAIN
nephroblastoma	kidney
RETINOBLASTOMA	RETINA of the EYE
osteoblastoma	BONE
neuroblastoma	NERVOUS SYSTEM tissue
glioblastoma multiforme (GBM)	brain

See also ADENOCARCINOMA; CARCINOMA; LEUKEMIA; SARCOMA; SURGERY FOR CANCER; SURGERY BENEFIT AND RISK ASSESSMENT; WILMS'S TUMOR.

BRCA-1/BRCA-2 BREAST CANCER GENE 1 and breast cancer gene 2, the first genes in which researchers identified mutations that correlate to increased susceptibility to BREAST cancer and OVARIAN CANCER. About one in six women who have either of these cancers have mutations in either or both of the genes. Many are women who have a known family history of breast cancer or ovarian cancer. The presence of mutations in either of these genes means a woman has an increased risk for developing breast or ovarian cancer but it does not mean cancer is inevitable. Researchers do not yet know the extent to which BRCA-1/BRCA-2 gene mutations affect a woman's risk for cancer, though believe they are responsible for about 5 percent of breast and ovarian cancers. Many factors influence the development of cancer; genetics remains only one among them.

Testing for BRCA-1/BRCA-2 is controversial because there are few preventive or therapeutic actions women or doctors can take as a result of knowing a positive result. Under current practice guidelines, doctors may choose to offer such testing to women who have first-degree relatives (mother, daughter, sister, grandmother) who have breast cancer or ovarian cancer or who are themselves under age 50 at the time of being diagnosed with either type of cancer. A positive result (mutations are present) may be a factor in prophylaxis or treatment decisions, though is by itself not a strong enough indicator to be the basis for such decisions. Nor is a negative result any indication that a woman will not develop breast or ovarian cancer. Because doctors can detect breast and ovarian cancers early through regular examinations, most health experts believe such examinations remain the most effective means for early diagnosis and treatment regardless of genetic influences.

See also CA-125; GENETIC TESTING; MUTATION; PROSTATE-SPECIFIC ANTIGEN (PSA).

C

cancer risk factors The circumstances that may increase an individual's chance for developing cancer. Cancer risk is a combination of hereditary, environmental, viral, bacterial, immunologic, and lifestyle factors that alter CELL STRUCTURE AND FUNCTION. Age is the most significant single risk factor for cancer, with most cancer developing in people age 50 and older. This reflects current thinking that most cancer results from cumulative damage to cellular DNA, which causes changes in cells as they divide.

Gender is a significant risk factor for specific cancers. For example, BLADDER CANCER is three times more common in men than women, and only about 1 percent of BREAST CANCER occurs in men. Ovarian and endometrial cancers are uniquely women's cancers, and TESTICULAR CANCER and PROSTATE CANCER are uniquely men's cancers. LIVER CANCER and PANCREATIC CANCER are also more common in men. Hereditary genetic factors influence the risk for breast cancer, ovarian cancer, and COLORECTAL CANCER.

The most significant mutable (changeable) risk factor for cancer is cigarette smoking, which accounts for 85 percent of LUNG CANCER, 60 percent of bladder cancer, and about 30 percent of other cancers collectively. Excessive ALCOHOL consumption and exposure to environmental carcinogens (substances that cause cancer) are also preventable risks for cancer.

Infectious agents are emerging as major risk factors for certain cancers. Researchers have already linked certain cancers with specific infections. More than 90 percent of women who have CERVICAL CANCER also have HUMAN PAPILLOMAVIRUS (HPV) INFECTION. About 80 percent of people who have STOMACH CANCER test positive for the presence of *HELICOBACTER PYLORI*, which causes a low-grade bacterial infection in the stomach. In Western cultures, KAPOSI'S SARCOMA occurs nearly exclusively in people who have HIV/AIDS.

See also BACTERIA; BRCA-1/BRCA-2; CANCER PREVENTION; COLONOSCOPY; MAMMOGRAM; PARASITE; PROSTATE-SPECIFIC ANTIGEN (PSA); SMOKING AND HEALTH; VIRUS.

cancer treatment options and decisions The methods and protocols available to treat cancer and its symptoms. Most cancer treatment involves a combination of methods. There are a number of conventional treatment options for cancer:

- SURGERY FOR CANCER, in which the doctor performs an OPERATION to remove the cancer, is the treatment of first choice for most solid tumors (cancer that develops in organs and tissues other than the BLOOD, LYMPH, or BONE MARROW). The surgery generally removes the tumor and a safe margin of healthy tissue surrounding the tumor in the attempt to prevent stray cells at the tumor's periphery from migrating into other tissues. Sometimes the operation to remove the cancer involves removing an entire structure or organ to obtain such a margin.
- RADIATION THERAPY may precede or follow surgery or may be the sole or an adjuvant treatment. Radiation therapy targets high-energy particles at the cancer cells. The energy—radiation—disrupts the ability of the cancer cells to grow and divide. The cells die, and the body's natural mechanisms (such as PHAGOCYTOSIS) eliminate their debris. Radiation before surgery shrinks the tumor. The main purpose of radiation therapy after surgery is to kill any lingering or stray cancer cells. The oncologist may also combine radiation therapy with CHEMOTHERAPY

CANCER RISK FACTORS

Risk Factor	Type of Cancer
age 50 years and older	all cancers
ALCOHOL consumption	STOMACH CANCER, LIVER CANCER, PANCREATIC CANCER
cigarette smoking	cancers of the lung, BLADDER, kidney, STOMACH, BREAST, prostate, COLON, PANCREAS; acute myeloid LEUKEMIA (AML)
EPSTEIN-BARR VIRUS	Burkitt's lymphoma
gender: female	BREAST CANCER, ENDOMETRIAL CANCER, CERVICAL CANCER
gender: male	BLADDER CANCER, PROSTATE CANCER, pancreatic cancer, stomach cancer, CANCER OF THE PENIS, TESTICULAR CANCER, liver cancer
HELICOBACTER PYLORI INFECTION	stomach cancer, gastric lymphoma
HEPATITIS B VIRUS/hepatitis C virus	liver cancer
HIV/AIDS	KAPOSI'S SARCOMA, lymphoma
human herpes virus-8 (HHV-8)	Kaposi's sarcoma
HUMAN PAPILLOMAVIRUS (HPV) infection	cervical cancer, cancer of the PENIS, vaginal cancer, anal cancer, cancer of the VULVA
human T-lymphotropic virus-1 (HTLV-1)	adult T-cell leukemia/lymphoma (ATL)
INFLAMMATORY BOWEL DISEASE (IBD)	COLORECTAL CANCER
INTESTINAL POLYP	colorectal cancer
personal or family history of cancer	all, though notably breast, ovarian, and colorectal cancers
Schistosoma haematobium parasitic infection	bladder cancer
sun exposure	SKIN CANCER: basal cell CARCINOMA, squamous cell carcinoma, malignant melanoma
TOBACCO USE OTHER THAN SMOKING	oral cancer (lips, tongue, other structures of the MOUTH)

or IMMUNOTHERAPY for an additive effect. Adverse side effects generally stay localized (remain in the area exposed to the radiation).

- Chemotherapy uses drugs to kill cancer cells. Like radiation therapy, chemotherapy may precede or follow surgery to shrink tumors or kill residual cancer cells, serve as the sole treatment, or function as an adjuvant treatment in combination with other treatment methods for optimal effectiveness against certain types of cancer. Because chemotherapy affects the entire body, it can have significant side effects.
- Immunotherapy, also called biological response modification, uses methods to enhance the ability of the body's natural IMMUNE SYSTEM functions to target cancer cells for containment and destruction. Genetically engineered substances such as MONOCLONAL ANTIBODIES (MABS), INTERFERONS, and INTERLEUKINS are among the immunotherapy agents oncologists may administer to boost the IMMUNE RESPONSE.
- HORMONE THERAPY targets HORMONE-driven cancers such as PROSTATE CANCER, OVARIAN CANCER, ENDOMETRIAL CANCER, and BREAST CANCER. These cancers require hormones, typically ESTROGENS or TESTOSTERONE, to grow. Treatment either suppresses or boosts the presence of these hormones in the body. HORMONE THERAPY for breast cancer, for example, deprives the woman's body of estrogen or the ability to use it, and hormone therapy for prostate cancer deprives the man's body of testosterone or the ability to use it. Hormone therapy for prostate cancer may also include administration of estrogen in a further effort to shut down the tumor's hormone sources.
- BONE MARROW TRANSPLANTATION is a treatment option for LEUKEMIA, MULTIPLE MYELOMA, and lymphoma. BONE marrow transplantation replaces cancerous bone marrow with healthy marrow from a genetically matched donor called an allogeneic transplants (a syngeneic transplant when the donor is an identical twin). An autologous transplant uses the patient's own bone marrow, which is an option only when the cancer is in remission or when it does not involve the bone marrow. Bone marrow transplantation may sometimes be a treatment option for other types of cancer though has not proven to be as effective as originally hoped.
- Stem cell transplantation may be a treatment option in cancers that do not involve the bone marrow. The person's stem cells (precursors for red blood cells, white blood cells, and platelets) are gathered from the person's blood, then reinfused into the person after CHEMOTHERAPY.

Though there are established approaches, called treatment protocols, for most types of cancer, cancer treatment is highly individualized and treatment decisions evolve as a collaboration between the person who has cancer and the health-care team providing care for the person. The treatment decision process begins with consideration of the cancer's type, stage, and grade—the characteristics of the cancer cells, how widespread within the body the cancer is, and how aggressive the cancer cells are in their growth pattern. Other important factors include the person's age and overall health status, any other health conditions, and the person's preferences or goals for treatment.

INFORMATION MANAGEMENT

Because there is so much information to absorb and sort through when it comes to CANCER TREATMENT OPTIONS AND DECISIONS, it is a good idea to have a trusted family member or friend go along for key doctor visits to take notes. This lets the patient focus on the discussion with the doctor during the visit with the opportunity to later go over the notes and consider the options.

Sometimes there are clear "best" choices for treatment. Other times there are several treatment options that are likely to produce similar results. A person whose cancer is widespread (metastatic) by the time of diagnosis may choose only palliative treatment—treatments to relieve PAIN and other symptoms—or may choose to enter a clinical trial, a research study evaluating a new treatment that shows promise for the person's particular type or stage of cancer. Each treatment method has benefits and risks, which are important to consider when evaluating the various options.

A second opinion consultation from another oncologist (cancer specialist) is often helpful when there are numerous treatment options or when

treatment options appear slim. Different oncologists may view the same person's situation differently based on their level of experience and knowledge of specific cancers or treatments. Oncologists who practice through medical centers affiliated with research facilities, such as are common at large universities that have medical schools, often know of the newest drugs and therapies under evaluation in current or upcoming clinical trials.

There is an abundance of information about cancer available on the Internet and in publications; sorting through it all to determine what is reliable and what is potentially useful for an individual is confusing and often overwhelming. Because there are no controls over the content of Web sites in particular, a large amount of information is, unfortunately, inaccurate or potentially harmful; with the emotional factors that surround a cancer diagnosis, it is important to make treatment decisions based on sound principles. Many cancer treatment centers have staff and resources to help people put such information into contexts that are relevant for their personal situations. The American Cancer Society (www.cancer.org) and the US National Institutes of Health's (NIH's) National Cancer Institute (www.cancer.gov) provide numerous resources to help people sort through treatment claims and methods.

See also ALTERNATIVE AND COMPLEMENTARY REMEDIES FOR CANCER; BLOOD STEM CELLS; CANCER PREVENTION; COPING WITH CANCER; DIAGNOSING CANCER; END OF LIFE CONCERNS; QUALITY OF LIFE; STEM CELL; SURGERY BENEFIT AND RISK ASSESSMENT.

cancer vaccines Preventive therapies to keep cancer from developing in people who do not have it or to keep cancer from growing or recurring in people who have it. Most cancer vaccines remain in clinical trials. Two approved by the US Food and Drug Administration (FDA) are those for HEPATITIS B VIRUS (HBV), the virus primarily responsible for LIVER CANCER, and for some types of HUMAN PAPILLOMAVIRUS (HPV), the virus primarily responsible for CERVICAL CANCER. Preventing the viral infection nearly eliminates the risk for developing the cancer.

The HBV vaccine is among the recommended childhood vaccines in the United States, given as a series of three shots in infancy. Adults may also receive the HBV vaccine. Health experts recommend routine HPV vaccination for girls between ages 11 and 12, and for all young women to age 26. The HPV vaccine is a series of three injections given over 6 months. The vaccine protects against infection with HPV types 6 and 11, which cause genital warts, and types 16 and 18, which can cause cervical cancer. Both vaccines are effective indefinitely. However, the HPV vaccine is not effective in women who already have HPV infection.

Therapeutic cancer vaccines target an individual's cancer specifically, using antigens from the cancer cells to stimulate an IMMUNE RESPONSE against those cells. The laboratory makes a vaccine using cancer cells from the person. These cells contain the antigens for which the vaccine will stimulate the IMMUNE SYSTEM to produce antibodies. Therapeutic vaccines showing promise in clinical trials target PROSTATE CANCER, some types of BREAST CANCER, some types of LYMPHOMA, and some types of LUNG CANCER.

See also ANTIBODY; ANTIGEN; CANCER TREATMENT OPTIONS AND DECISIONS.

CA-125 Cancer ANTIGEN 125, a protein often elevated in the BLOOD circulation when certain cancers are growing in the body. The cells of the OVARIES, UTERUS, and FALLOPIAN TUBES produce CA-125; consequently CA-125 levels rise in OVARIAN CANCER, ENDOMETRIAL CANCER (cancer of the uterus), and CERVICAL CANCER. The most pronounced elevation occurs with ovarian cancer. However, numerous factors other than cancer can produce elevated CA-125 levels, including benign OVARIAN CYST and UTERINE FIBROIDS. Though an elevated CA-125 level may be one of numerous diagnostic factors the doctor considers when evaluating the possibility of a cancer diagnosis, this tumor marker by itself is not a reliable indicator of cancer. A blood test measures CA-125.

See also CARCINOEMBRYONIC ANTIGEN (CEA); GENETIC TESTING; ONCOGENES; PROSTATE SPECIFIC ANTIGEN (PSA); TUMOR MARKERS.

carcinoembryonic antigen (CEA) A protein present in the BLOOD circulation with certain types of cancer. In this regard, CEA serves as a tumor

marker. The cancers associated with elevated blood CEA levels are carcinomas of the COLON and RECTUM (COLORECTAL CANCER), PANCREAS, STOMACH, BREAST, and lung. The developing fetus also produces CEA, as do benign (noncancerous) tumors of the gastrointestinal tract. In these circumstances the presence of CEA in the blood circulation is normal and not an indication of cancer. Cigarette SMOKING AND CANCER treatment with CHEMOTHERAPY or RADIATION THERAPY also can produce elevated blood levels of CEA.

See also BREAST CANCER; CA-125; CARCINOMA; LUNG CANCER; PANCREATIC CANCER; STOMACH CANCER; TUMOR MARKERS.

carcinogen A substance that can cause cancer. The most common carcinogen is cigarette smoke, which is implicated in nearly all types of cancer and most specifically LUNG CANCER, BREAST CANCER, PROSTATE CANCER, pharyngeal cancer, STOMACH CANCER, and COLORECTAL CANCER. Other significant carcinogens include

- radon, a naturally occurring gas that results from the deterioration of naturally occurring uranium ubiquitously present in rocks and soil
- radiation, such as from overexposure to sunlight (ultraviolet) or ionizing radiation such as X-RAY and gamma-ray
- industrial chemicals such as benzene, vinyl chloride, and arsenic
- pharmaceutical agents such as hormones (oral contraceptives, estrogen supplements)

Some substances are beneficial in small amounts and carcinogenic in large amounts or in cumulative exposure over time, such as sunlight. Certain medications, notably IMMUNOSUPPRESSIVE MEDICATIONS and estrogen-containing drugs, may cause cancer. Others are hazardous at nearly any exposure level. CHEMOTHERAPY drugs, which effectively treat and cure many types of cancer, are themselves carcinogenic for certain types of LEUKEMIA and LYMPHOMA. RADIATION THERAPY as well increases the risk for subsequent cancers, depending on the site of irradiation. Pathogens such as viruses and BACTERIA cause certain kinds of cancer.

Limiting exposure to carcinogens reduces the likelihood that they will have adverse health effects. In the United States, federal and state regulations provide guidelines for occupational exposure to carcinogens. Other public health measures attempt to reduce carcinogen exposure through educational efforts.

COMMON CARCINOGENS

aflatoxins	arsenic
asbestos	benzene
beryllium	cadmium
chromium	cigarette smoke
cyclosporine	diethylstilbestrol (DES)
EPSTEIN-BARR VIRUS	ESTROGENS
ethylene oxide	formaldehyde
HELICOBACTER PYLORI	HEPATITIS B VIRUS
HUMAN PAPILLOMAVIRUS (HPV)	iodine-131
ionizing radiation	methyl chloride
radon	sunlight
tobacco	vinyl chloride

See also ASBESTOSIS; BERYLLIOSIS; CANCER PREVENTION; CANCER RISK FACTORS; ENVIRONMENTAL CIGARETTE SMOKE; ENVIRONMENTAL HAZARD EXPOSURE; LIFESTYLE AND CANCER; OCCUPATIONAL HEALTH AND SAFETY; PATHOGEN; RADON EXPOSURE; SMOKING AND CANCER.

carcinoma A cancerous tumor that arises from epithelial cells. Epithelial cells form the surface layer of tissue throughout the body: the SKIN, mucous membranes, and serous membranes (lining of the internal body cavities). Carcinoma is the most common form of cancer. A carcinoma generally carries the name of the tissue or site of its origin; for example, basal cell carcinoma originates in the basal cells of the skin and ADENOCARCINOMA originates in a glandular structure. Treatment depends on the nature, location, and size of the carcinoma and may incorporate surgery, CHEMOTHERAPY, RADIATION THERAPY, and IMMUNOTHERAPY.

TYPES OF CARCINOMA

Tumor	Location
ADENOCARCINOMA	glandular tissue
basal cell carcinoma	SKIN
intraductal carcinoma	BREAST
large-cell carcinoma	lung
lobular carcinoma	BREAST
small-cell carcinoma	lung
squamous cell carcinoma	skin, mucous membranes

See also ADENOMA; ADENOMA-TO-CARCINOMA TRANSITION; BLASTOMA; SARCOMA; SKIN CANCER.

chemotherapy Treatment for cancer that uses cytotoxic drugs (drugs that destroy cells) to kill cancer cells. About half of people who have cancer receive chemotherapy. Chemotherapy is commonly the treatment of first choice for LEUKEMIA, lymphoma, MULTIPLE MYELOMA, metastatic cancers, inoperable cancers, and as adjuvant therapy following or accompanying another method, such as surgery, that is the primary treatment. Sometimes chemotherapy is an appropriate choice for palliative treatment that shrinks cancer tumors to relieve symptoms such as PAIN. The goal of chemotherapy may be to eradicate the cancer or to keep the cancer in check to eliminate its symptoms and keep it from spreading.

How Chemotherapy Works to Treat Cancer

Chemotherapy drugs, also called chemotherapeutics or antineoplastic ("against new growth") drugs, work by interfering with cell growth, activity, or division. Many of them directly damage DNA, the cell's GENETIC CODE that directs the cell's processes for growth and replication. Chemotherapy drugs are toxic to all cells in the body. However, they have the most significant action on cells that are rapidly dividing, such as cancer cells. Most chemotherapy drugs have a NARROW THERAPEUTIC INDEX (NTI); there is a fine margin between their helpful and harmful actions. This narrow margin often causes unpleasant but predictable side effects that subside at the end of treatment.

Chemotherapy Agents

More than 600 chemotherapy drugs are currently available to oncologists, who often combine them in dozens of treatment protocols to treat various types of cancer. Chemotherapy drugs may be administered by MOUTH (oral), injection (intravenous, intramuscular, or subcutaneous), local application (topical or via instilled solution such as into the BLADDER), and intrathecal catheter (into the spinal canal).

Alkylating agents The alkylating agents are the oldest type of chemotherapy drugs and derive from nitrogen mustards, the chemical family to which poisonous mustard gas belongs. These chemotherapy drugs interfere with at least four stages of cell division, making them highly effective against many types of cancer. Consequently many chemotherapy protocols include an alkylating agent. Some of the alkylating agents require METABOLISM by CYTOCHROME P450 (CYP450) ENZYMES, a large group of enzymes in the LIVER that metabolize many kinds of drugs, to be effective. Many factors, including genetic encoding and diet, affect the function and efficiency of CYP450 enzymes.

COMMON ALKYLATING AGENTS

busulfan	carmustine
chlorambucil	cyclophosphamide
dacarbazine	iphosphamide
lomustine	mechlorethamine
melphalan	procarbazine
thiotepa	

Antimetabolites The antimetabolites derive from chemical structures similar to vitamins and amino acids (called metabolites) though are useless to cells. The chemical similarity is so close, however, that cells mistake antimetabolites for substances they need to carry out their metabolic processes. However, the antimetabolites cannot complete those metabolic processes, interfering with the ability of cells to synthesize (make) nucleic acid, an essential component of DNA. Without new DNA, cells cannot divide. Though each antimetabolite agent has specific cancers against which it is most effective, as a group the antimetabolites are particularly effective in treating leukemia, lymphoma, COLORECTAL CANCER, BREAST CANCER, BLADDER CANCER, PANCREATIC CANCER, and osteosarcoma. Antimetabolites have numerous side effects, including NAUSEA, HAIR loss, and tubular nephritis (damage to the KIDNEYS). Oncologists may give leucovorin along with the antimetabolite to counter these side effects.

COMMON ANTIMETABOLITES

6-mercaptopurine	6-thioguanine
arabinosylcytosine	capecitabine
cladiribine	cytarabine
dacarbazine	fludarabine
fluorouracil (5-FU)	gemcitabine
methotrexate	

Antibiotic chemotherapy agents The anthracyclines and the related DRUG bleomycin are antibiotics that come from the FUNGUS *Streptomyces verticillus,* which naturally occurs in soils primarily in Japan though also can be cultivated. These chemotherapy drugs work by forming free radicals that disrupt the structure of cellular DNA. They are particularly effective against leukemia, lymphoma, and many types of CARCINOMA, notably breast cancer. Bleomycin is similar to the anthracyclines, derived also from the *S. verticillus* fungus, but a different chemical composition and action in cells. It is most effective in combination with other chemotherapy agents for treating lymphoma and TESTICULAR CANCER. The most significant SIDE EFFECT of the anthracyclines is damage to the HEART, and of bleomycin damage to the LUNGS, as a result of free radical activity.

COMMON ANTIBIOTIC CHEMOTHERAPY AGENTS	
bleomycin	dactinomycin
daunorubicin	doxorubicin
epirubicin	idarubicin
mitoxantrone	

Camptothecins, etoposide, and vinca alkaloids The camptothecins block the function of topoisomerase, an enzyme cells need to synthesize DNA. Their original source was the bark of the *Camptotheca acuminata* tree native to China. Etoposide has the same action but comes from the bark of the mandrake tree. Vinca alkaloids derive from the leaves of the *Vinca rosea* plant, a type of periwinkle. The vinca alkaloids disrupt cell division. Like the alkylating agents, the camptothecins, etoposide, and vinca alkaloids are effective in treating a broad spectrum of cancers from leukemia and lymphoma to carcinomas and some sarcomas.

COMMON CAMPTOTHECINS, ETOPOSIDE, AND VINCA ALKALOIDS	
etoposide	vincristine
vinblastine	vinorelbine
irinotecan	topotecan

Taxanes The taxanes come from the bark of the *Taxus brevifolia*—the Pacific yew tree. They work as chemotherapy agents by blocking the ability of cells to form the structures necessary to divide. They also appear to enhance a number of immune functions and are particularly effective in treating some types of metastatic breast cancer. Currently there are two taxanes, each of which is often more effective in combination with other chemotherapy agents than alone. As well, each taxane has specific side effects: docetaxel can cause severe EDEMA (fluid retention) and paclitaxel can cause MUSCLE pain. Both drugs can cause NEUROPATHY (dysfunction of the nerves) and severe depletion of neutrophils (NEUTROPENIA), white BLOOD cells (leukocytes) important for fighting INFECTION. Neutropenia raises the risk for infection.

TAXANES
docetaxel
paclitaxel

Platinum compounds Platinum compounds disrupt cellular DNA function as well as the ability of cells to synthesize DNA. These chemotherapy agents are particularly effective in treating LUNG CANCER, testicular cancer, and colorectal cancer. They can cause kidney damage and neuropathy.

PLATINUM COMPOUNDS		
carboplatin	cisplatin	oxaliplatin

Risks, Side Effects, and Complications of Chemotherapy

Because chemotherapy is a systemic treatment, it affects all cells in the body. Those most severely affected are those that grow and divide rapidly. Though cancer cells are at the head of that list, some healthy cells in the body also grow and divide rapidly. Among them are the cells of hair follicles (which produce hair), blood, and gastrointestinal tract, accounting for the most significant side effects of chemotherapy: hair loss, ANEMIA, increased susceptibility to infection, nausea, VOMITING, and DIARRHEA. However, the extent to which these side effects occur varies across the spectrum of chemotherapy drugs, and many people receiving chemotherapy do not experience them.

Medications and complementary remedies such as GINGER may help with chemotherapy-related nausea. ACUPUNCTURE also provides relief from nausea and other discomforts. Antinausea medica-

tions in the 5-HT3 receptor antagonist family (dolasetron, granisetron, ondansetron, and palonosetron) are especially effective. The long-term risks of chemotherapy include increased likelihood of developing another cancer, notably lymphoma or leukemia (especially acute myeloid leukemia with alkylating agents). Repeated chemotherapy, such as with chronic cancers or multiple recurrences, damages and may destroy the BONE MARROW.

HAIR LOSS DURING CHEMOTHERAPY

The cells of the HAIR follicles divide rapidly and thus are highly susceptible to the effects of chemotherapy. Because of this, people lose their hair after undergoing chemotherapy. However, because hair follicle cells are healthy and normal in their structure and function, most of them are able to resume growth and division—and hair production—when chemotherapy ends.

See also ANTIBIOTIC MEDICATIONS; CELL STRUCTURE AND FUNCTION; INVESTIGATIONAL DRUGS; LEUKOCYTE; PHARMACODYNAMICS; PHARMACOKINETICS; RADIATION THERAPY; SURGERY FOR CANCER.

coping with cancer Methods for handling the physical, emotional, financial, and other stresses of a cancer diagnosis. The diagnosis of cancer is a life-altering event, no matter the type of cancer and its prognosis. Few other health conditions evoke such intense emotions. Though each individual responds uniquely, cancer evokes in everyone a recognition of vulnerability and mortality. It is important for each individual to be able to express his or her feelings, fears, anger, worries, and hopes. Some people want to talk about their cancer and their feelings, some people deny their diagnosis or its seriousness, and some people retreat to introspection.

The time of treatment is often very intense, with most of the focus in the person's life shifting to the treatment and its myriad details. Many people find themselves suddenly and completely immersed in an existence that revolves around doctors, hospitals, tests, and procedures. There may be concerns about health insurance coverage or payment for doctor bills, hospital services, treatment, and medications. Hospitals have financial counselors and social workers who can help work through details such as preauthorizations, coverage requirements, and private and government programs that subsidize or pay for care for people who lack the resources.

Many people are able to return to full, active lives after cancer treatment, and their outward appearance may seem the same as before the diagnosis. However, coping with cancer is a lifelong process for most people. Even when treatment concludes, residual effects may remain as reminders of the cancer. People who had surgery have visible scars and may have deformities, NERVE damage, BLOOD vessel or circulatory disruptions, LYMPHEDEMA, or alterations such as COLOSTOMY or reconstruction. As well, there often are ongoing health-care needs, such as doctor visits, medications, blood tests, and imaging procedures. Most people worry, no matter how healthy they are or how many years go by after treatment, about the possibility that the cancer could come back.

No one expects a diagnosis of cancer; when it strikes, it completely disrupts the fabric of everyday life. The cancer diagnosis also affects family members, friends, and co-workers. The person who has cancer must decide who, and how much, to tell about the cancer. Often, treatment requires time away from work and the person may not be able to return to full work activities for quite some time. People who have young children at home are likely to need extended help from family and friends during treatment and recovery. Older people who live alone may also need support with transportation, housekeeping, and cooking.

Despite the all-consuming nature of cancer diagnosis and treatment, it is important for the person to remain engaged in activities of life that bring relaxation, comfort, and joy, such as spending time with family and friends, participating in favorite recreations and hobbies, or traveling. Many people find peace and calm in YOGA, MEDITATION, or prayer. Because there are dimensions to having cancer that only other people who have cancer can fully understand, SUPPORT GROUPS provide a way for the person who has cancer to share their feelings and experiences.

See also LIFESTYLE AND HEALTH; QUALITY OF LIFE.

D

diagnosing cancer The procedures and tests that determine whether cancer is present. The diagnostic journey often begins with an unusual finding on a screening procedure, such as a MAMMOGRAM or PROSTATE SPECIFIC ANTIGEN (PSA) BLOOD test, or diagnostic procedure done for another purpose such as an X-RAY or a complete blood count (CBC). Sometimes the person identifies symptoms, such as the presence of a lump or rectal bleeding.

The initial doctor's evaluation includes a thorough ROUTINE MEDICAL EXAMINATION with specific focus on the abnormal findings; comprehensive PERSONAL HEALTH HISTORY; and appropriate diagnostic tests, which may include any combination of blood tests, X-rays, COMPUTED TOMOGRAPHY (CT) SCAN, POSITRON EMISSION TOMOGRAPHY (PET) SCAN, MAGNETIC RESONANCE IMAGING (MRI), ULTRASOUND, and biopsy.

Biopsy provides the definitive diagnosis for cancer, giving the pathologist the opportunity to examine tissue structure and cell composition. Depending on the location, size, and characteristics of a tumor, the doctor may remove a small sample of tissue or remove the entire tumor. Common methods for sampling tumors include

- fine-needle aspiration, in which the doctor inserts a small needle into the tumor to withdraw a sample of fluid and cells
- core-needle biopsy, in which the doctor inserts a larger needle into the tumor to extract a core of solid tissue
- ENDOSCOPY, in which the doctor inserts an endoscope into the body through a natural opening to examine suspicious tissues and remove samples
- incisional biopsy, in which the surgeon removes a portion of the tumor to obtain a representative tissue sample
- excisional biopsy, in which the surgeon removes the entire tumor

The pathologist then determines, from the diagnostic tests, imaging procedures, and biopsy findings, the cancer's stage and grade—assessments of how extensive the presence of the cancer in the body and how aggressive the growth of the cancer cells. Though most cancers fit within the standard parameters of STAGING AND GRADING OF CANCER, some do not. The doctor may then present the circumstances and diagnostic findings to a review panel of physician specialists, often called the "tumor board," for additional input and assessment. All of these evaluations then help guide the CANCER TREATMENT OPTIONS AND DECISIONS.

See also CANCER PREVENTION; COLONOSCOPY; SURGERY BENEFIT AND RISK ASSESSMENT; SURGERY FOR CANCER.

diet and cancer The ways in which foods and NUTRIENTS influence the risk for cancer, cancer development, and the effectiveness of cancer treatment. A number of foods have emerged that appear to contain substances that have cancer-fighting capabilities. Substances found in foods that appear able to help the IMMUNE SYSTEM suppress the development and growth of cancer cells include calcium, folate (folic acid), carotenoids, vitamin C, flavonoids, lignans, lycopenes, catechins, indoles, and SOY isoflavones. Numerous foods provide these substances. Conversely, foods that are high in saturated fat, highly salted foods,

FOODS THAT SUPPLY CANCER-FIGHTING SUBSTANCES

Cancer-Fighting Substance	Cancer-Fighting Actions	Food Sources
calcium	reduces the irritation bile and fatty acids cause in the gastrointestinal tract particular benefit to reduce risk for COLORECTAL CANCER	broccoli, bok choy, kale, milk, yogurt, cheese, salmon, legumes
carotenoids (beta-carotene, lutein, zeaxanthin)	block growth of cancer cells particular benefit to reduce risk for LUNG CANCER and CERVICAL CANCER	carrots, sweet potatoes, yellow squash, apricots, bell peppers, corn, spinach
catechins	neutralize free radicals	GREEN TEA, grapes, wine, chocolate
flavonoids	protect DNA, neutralize free radicals	carrots, citrus fruits, onions, apples, tomatoes, blueberries, broccoli, soybeans and soybean products
folate (folic acid)	essential for DNA synthesis and repair	beets, broccoli, cabbage, legumes, spinach, avocados, turkey, asparagus
indoles	block the actions of carcinogens to cause cells to mutate particular benefit to reduce risk for BREAST CANCER and PROSTATE CANCER	cauliflower, Brussels sprouts, bok choy, cabbage, broccoli
lignans	maintain cell health particular benefit to reduce risk for breast cancer, colorectal cancer, and prostate cancer	flaxseed oil, flaxseeds, whole grains, pumpkin seeds, cranberries, green tea, black tea
lycopenes	particular benefit to reduce risk for prostate cancer	tomatoes, tomato sauce, pink grapefruit, guava, watermelon
soy isoflavones	block tyrosine kinase, an enzyme that promotes cancer cell proliferation particular benefit to reduce risk for HORMONE-DRIVEN CANCERS (breast cancer, prostate cancer, OVARIAN CANCER, and ENDOMETRIAL CANCER)	fresh soybeans, tofu, soy flour, soy-based foods
vitamin C	ANTIOXIDANT that neutralizes free radicals blocks conversion of nitrates blocks cancer cells from dividing and proliferating particular benefit to reduce risk for ESOPHAGEAL CANCER and STOMACH CANCER	citrus fruits, strawberries, red cabbage, bell peppers, kiwi fruit, mangoes

and preserved foods appear to increase the risk for cancer overall and particularly for cancers of the gastrointestinal tract.

The extent to which nutrients can inhibit tumor growth remains an area of intensive study in CANCER PREVENTION research. Though foods and nutrients are not the sole factors that prevent or cause cancer, they clearly play significant roles in immune function.

See also CANCER RISK FACTORS; DIET AND HEALTH; EXERCISE AND HEALTH; LIFESTYLE AND CANCER; LYCOPENE.

dysplasia Abnormal changes that are occurring in cells. In dysplasia, rapidly dividing cells form tissue that has an anomalous structure. This structure has the potential of transitioning to cancer. Dysplasia is an early stage of development for all cancers but not all dysplasia becomes cancer. Because there is no way to know which direction dysplasia will go, doctors closely monitor and often surgically remove or otherwise treat dysplasia. ROUTINE MEDICAL EXAMINATION or health screening commonly detects dysplasia, which seldom produces symptoms. Frequently identified dysplasias include cervical dysplasia, which affects a woman's CERVIX, and oral dysplasia, which affects the mucous membranes in the MOUTH.

Doctors classify dysplasia according to the extent of disruption within the tissue. The earliest stage of dysplasia is hyperplasia, in which cells are growing more rapidly than normal but the structural integrity of the tissue remains normal. In mild dysplasia, the excessive cell growth produces erratic and abnormal tissue structure. In severe dysplasia, also called cancer in situ, cell growth and tissue structure are significantly abnormal but the irregularity remains confined to a single site. The risk for cancer in situ to evolve into a full cancer is high.

Treatment for dysplasia depends on the severity and location of the dysplasia as well as other health factors—such as smoking, which increases risk for all types of cancer—or a condition such as INFECTION with HUMAN PAPILLOMAVIRUS (HPV), which increases risk for cervical cancer. Mild dysplasia may revert to normal growth; often the doctor will recommend diligent observation with examination every three to six months to monitor cell activity at the site. Electrocautery (burning), cryotherapy (freezing), laser ablation, and surgical excision are among methods for eradicating dysplasia. Dysplasia may recur, depending on its cause, though in most circumstances does not return after treatment.

See also CELL STRUCTURE AND FUNCTION; LASER SURGERY; PAP TEST.

hormone-driven cancers Types of cancer that thrive on or require hormones for their survival. In men, ANDROGENS (notably TESTOSTERONE) sustain PROSTATE CANCER. In women, ESTROGENS and PROGESTERONE feed many types of BREAST CANCER, OVARIAN CANCER, and ENDOMETRIAL CANCER (cancer of the UTERUS).

Hormone-driven cancers arise in cells that are HORMONE dependent. However, researchers do not know whether hormones cause these cancers to develop or simply fuel them after they form. Researchers do know that breast cancer and ovarian cancer occur more often in women who have extended exposure to estrogen, such as with early onset of MENSTRUATION (MENARCHE before age 12) or late MENOPAUSE (after age 55). The use of oral contraceptives (birth control pills) or hormone replacement therapy (HRT) for menopause may also increase a woman's risk for these cancers, though research continues to investigate these connections.

The correlation between hormones and cancer becomes even less distinct with prostate cancer. Researchers know that testosterone fuels the growth of prostate cancer cells once the cancer develops. But the role of testosterone in the development of prostate cancer is unknown. Unlike estrogen and progesterone levels in women, testosterone levels in men are fairly constant though do decline gradually after age 30. Some researchers believe it is lower testosterone levels that allow prostate cells to mutate, becoming cancerous. Other researchers believe the changing balance between estrogen and testosterone in a man's body as he ages plays a contributing role. Hormone-driven cancers in men and women are more likely after age 50.

HORMONE THERAPY as adjuvant therapy is the standard of care for most hormone-driven cancers. Primary treatment may be surgery to remove the tumor, RADIATION THERAPY, or CHEMOTHERAPY, or a mix of any or all of these treatment options. Oncologists use luteinizing hormone–releasing hormone (LHRH) agonists, which suppress the body's production of androgens and estrogens, to treat prostate cancer in men and breast, ovarian, and endometrial cancers in women. Aromatase inhibitors, which block the body's ability to convert androgens to estrogen, and tamoxifen, which binds with estrogen receptors to block estrogen, are among the hormone therapies oncologists use to treat hormone-driven breast cancers in women.

See also CANCER TREATMENT OPTIONS AND DECISIONS; IMMUNOTHERAPY.

hyperplasia Overgrowth of cells. Hyperplasia, also called hypertrophy, may occur for various reasons. Though the overgrowth of tissue may cause symptoms it is not necessarily cancerous. For example, BENIGN PROSTATIC HYPERPLASIA (BPH) is common in men over age 65 and commonly causes symptoms such as difficult URINATION. Endometrial hyperplasia is similarly common in women approaching MENOPAUSE, causing symptoms such as abnormal uterine bleeding. Typically the structure of cells and tissue in hyperplasia is normal; there is simply an overgrowth. The risk is that hyperplasia will progress to abnormal cells and tissue structure, a precancerous condition called DYSPLASIA. Unless it causes symptoms, hyperplasia does not require treatment other than diligent monitoring.

See also CANCER RISK FACTORS; CELL STRUCTURE AND FUNCTION.

lifestyle and cancer Personal factors that may contribute to the prevention or the development of cancer. The most significant lifestyle factors related to cancer are smoking, diet, OBESITY, and exposure to environmental carcinogens.

Smoking and Other Tobacco Use

Cigarette smoking accounts for 87 percent of LUNG CANCER in the United States, making lung cancer one of the most preventable types of cancer. Cigarette smoking also raises the risk for numerous other types of cancer, including oral cancer, laryngeal cancer, ESOPHAGEAL CANCER, STOMACH CANCER, LIVER CANCER, COLORECTAL CANCER, PANCREATIC CANCER, kidney cancer, BLADDER CANCER, PROSTATE CANCER, BREAST CANCER, and CERVICAL CANCER. Cigar smoking increases the risk for oral cancers (cancers of the MOUTH and lips) as well as lung cancer, pharyngeal cancer, and stomach cancer. Other tobacco use, such as chewing tobacco and snuff, is the primary cause of oral cancers. Not using any form of tobacco removes its risk as a cause of cancer.

Diet and Nutrition

Numerous studies indicate a diet high in fruits, vegetables, and whole grains and whole grain products reduces the risk for most cancers overall and specifically for esophageal cancer, stomach cancer, and colorectal cancer. Researchers believe the NUTRIENTS, antioxidants, and fiber are the key substances that lower cancer risk. Nutrients and antioxidants boost the IMMUNE SYSTEM, improving its ability to detect and eliminate abnormal cells early in their development. Fiber helps absorb toxins in the gastrointestinal tract and move them more rapidly through the digestive process.

Conversely, research demonstrates that a diet high in red meat increases the risk for cancer overall and specifically HORMONE-DRIVEN CANCERS and cancers of the gastrointestinal tract. Red meat is the primary dietary source of saturated fats, which the body uses to synthesize (make) steroid hormones (androgens and estrogens). These hormones fuel the growth of some types of cancer cells in breast cancer, OVARIAN CANCER, ENDOMETRIAL CANCER, and prostate cancer. Whether they may also encourage the development of these cancers remains under investigation.

Some research has established a connection between the length of time food remains in the gastrointestinal tract with the risk for colorectal cancer. A diet high in plant-based, high-fiber foods moves through the digestive process more quickly than a diet high in fat. Some studies show a primarily plant-based diet may move through the body in 6 to 8 hours, while a high-fat, low-fiber diet may take as long as 26 hours to make the digestive journey.

Obesity

The risk for numerous cancers rises with OBESITY. The reasons for this are difficult to separate out. Researchers know that regular physical activity and nutritious EATING HABITS support the health of cells throughout the body as well as foster efficient immune function. These factors are generally lacking in obesity. Further, the increase in adipose tissue prevalent in obesity appears to be a contributing factor to hormone-driven cancers such as prostate cancer and breast cancer, the risks for which are higher in people who have obesity than in people who are of healthy weight.

Exposure to Environmental Carcinogens

Researchers have identified more than a thousand chemicals and other substances that have the ability to cause cancer. Some become hazardous only with repeated excessive exposure over time, and some have a fairly immediate consequence. Chemical exposures are common causes of THYROID CANCER, LEUKEMIA, and LYMPHOMA. The ultraviolet rays of sunlight are perhaps the most common long-term environmental CARCINOGEN, responsible for nearly all SKIN CANCER. Radon, which is present in the soil as a byproduct of deteriorating uranium and other radioactive minerals that occur naturally, is the second-leading cause of lung cancer. RADIATION THERAPY as treatment for cancer is also a carcinogen, raising the risk for lymphoma as well as solid tumors.

Lifestyle Modifications to Decrease Cancer Risk

Nutritious eating habits, daily physical exercise, and avoidance of tobacco products are key ways in which people can modify their lifestyles to reduce the risk for cancer as well as other significant health conditions such as CARDIOVASCULAR DISEASE

(CVD) and DIABETES. Health experts recommend that all homes be tested for radon levels, as basements and foundations can trap radon that emerges from the underlying soil. There are ways to release trapped radon so it does not present a cancer risk. ROUTINE MEDICAL EXAMINATION helps detect precancerous conditions and cancer when it is in its early, treatable stages.

See also CANCER PREVENTION; CANCER RISK FACTORS; DIET AND CANCER; HEALTH RISK FACTORS; RADON EXPOSURE; SMOKING AND CANCER; WEIGHT LOSS AND WEIGHT MANAGEMENT.

M–O

metastasis Cancer that spreads beyond its site of its origin. Metastasis may be local (extend outside the original tumor but remain near the original site), regional (remain in the general vicinity of the original site), or distant (in organs or tissues elsewhere in the body from the original site). It may occur as a result of direct invasion of adjacent tissues and organs or when cancer cells enter the LYMPH or BLOOD circulation. A metastasized cancer retains the characteristics of the tumor of origin. For example, PROSTATE CANCER that metastasizes to the BONE is metastatic prostate cancer, not BONE CANCER. The type of cancer is an important factor in determining the most effective treatment. The LUNGS, LIVER, and bone are the most common sites for metastasis. Cancer that comes back after treatment is a RECURRENCE. Metastasis may be evident at the time of diagnosis or may occur after treatment.

See also CANCER TREATMENT OPTIONS AND DECISIONS; REMISSION.

molecularly targeted therapies Treatment approaches for cancer that interfere with specific molecular functions within cancer cells to prevent them from dividing. The most significant benefit of molecularly targeted therapies is that they can selectively alter the function of specific cancer cells without affecting the function of normal cells. They do so primarily by targeting the protein signals cancer cells use that regulate their growth and division. These signals may be ones that promote growth or regulate APOPTOSIS (natural cell death). The drugs that target them may be signal-transduction inhibitors (also called small-molecule drugs), apoptosis-inducing drugs, and MONOCLONAL ANTIBODIES (MABS).

Current molecularly targeted therapies are especially promising for cancers that have a widespread presence in a vital organ or throughout the body, such as small-cell LUNG CANCER (SCLC) and MULTIPLE MYELOMA, which makes them difficult to treat through other approaches. Because molecularly targeted therapies are so new, doctors do not know their risks or long-term consequences or the extent to which they may be effective in treating cancers in general.

DRUGS USED IN MOLECULARLY TARGETED THERAPIES

bortezomib (Velcade)	gefitinib (Iressa)
imatinib mesylate (Gleevec)	oblimersen (Genasense)
rituximab (Rituxan)	trastuzumab (Herceptin)

See also CANCER TREATMENT OPTIONS AND DECISIONS; CELL STRUCTURE AND FUNCTION; CHEMOTHERAPY; IMMUNOTHERAPY; ONCOGENES; TUMOR SUPPRESSOR GENES.

oncogenes Mutated proto-oncognes that abnormally infuence the rate of growth of cells. Researchers believe oncogenes play a role in the development of cancer by altering cellular growth through one or more mechanisms. Oncogenes may accelerate cell division, block APOPTOSIS (planned cell death), or in other ways allow cells to grow beyond the boundaries of the body's normal controls. MOLECULARLY TARGETED THERAPIES and MONOCLONAL ANTIBODIES (MABS) show significant promise for altering oncogenes to reduce their role in the development of cancer.

Proto-oncogenes are the normal genes which contain the genetic code that tells cells which proteins, and how much of them, to produce to direct the cell's own growth. These proteins, called sig-

naling proteins, act as messengers within the cell. When proto-oncogenes mutate, their genetic instructions become garbled. The protein production they regulate changes. The cell may produce too many proteins that instruct it to grow, or not enough proteins that instruct it to stop growing. In either circumstance the cell's growth becomes excessive.

Oncogenes do not alone cause cancer, though researchers remain uncertain about the extent to which they influence the development of cancer. Other genetic and environmental factors come into play, affecting various aspects of cellular growth. Mutations may occur in the genes that regulate DNA repair, for example, allowing damaged cells to replicate. Researchers believe it is the convergence of factors, the emergence of oncogenes among them that permits cancer to develop.

IDENTIFIED ONCOGENES

Gene	Cancer Connection
bcl-2	B-cell lymphoma and numerous other cancers
c-erb	BREAST CANCER
c-myc	small-cell LUNG CANCER (SCLA), Burkitt's lymphoma
HER-2/neu	breast cancer
hTERT	numerous cancers
ras	numerous cancers
src	breast cancer, colon cancer, SCLA, neuroblastoma, rhabdomyosarcoma

See also CELL STRUCTURE AND FUNCTION; TUMOR SUPPRESSOR GENES.

P

pain management in cancer The ability to improve comfort and provide relief from PAIN and related symptoms that cancer and cancer treatment may cause. Many people worry about the potential for their cancer to cause pain. However, the broad spectrum of available ANALGESIC MEDICATIONS and other methods provide numerous options to manage, and often entirely relieve, pain due to cancer.

Causes of Pain in Cancer

Pain in cancer arises from either the cancer or from treatments for the cancer. Cancerous tumors can cause pain when they invade tissues and disrupt the nerves. Sometimes cancer can also invade NERVE tissue, also causing pain. Damage to structures, such as may occur when cancer invades and destroys tissues and organs, causes the cells of those structures to release numerous CYTOKINES (biochemicals that activate various components of the IMMUNE RESPONSE). Among these cytokines are substances that stimulate nociceptors, specialized molecules in peripheral neurons that send pain signals to the CENTRAL NERVOUS SYSTEM. RADIATION THERAPY is often effective for pain relief in such situations, as it can shrink the tumor so it no longer pressures nerves and other structures. Sometimes surgery to remove part of the tumor also provides relief.

SURGERY FOR CANCER is most often the cause of treatment-related pain. Sometimes surgery for cancer is extensive, and the recovery period can be lengthy and challenging. Most people are eager to recuperate and return to their normal activities as quickly as possible. They may feel taking analgesic medications prolongs their recovery or may fear that taking narcotic medications, the strongest pain relievers, will result in ADDICTION. Neither is true. It may be necessary to take analgesic medications regularly and for an extended time after major cancer surgery to effectively manage the pain. This is important because adequate pain relief not only provides comfort but also allows the body to heal. Protracted pain is emotionally and physically stressful in ways that interfere with HEALING and QUALITY OF LIFE.

Analgesic Medications for Pain Relief

Over-the-counter analgesic medications such as NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) and acetaminophen often provide relief from mild to moderate discomfort and pain. Prescription NSAIDs and narcotic medications may be necessary for moderate to significant pain. Dependence and addiction are very seldom concerns in people who are taking narcotic pain relievers for such levels of pain. As well, there is little risk for overdose, another major concern.

Though there is a ceiling effect with NSAIDs (a point beyond which increasing the dose does not provide any greater pain relief), this is not the case with opioid analgesics. The body seems able to accommodate the effects narcotics have on the respiratory cycle when the narcotics are necessary to relieve high levels of pain. However, opioid pain relievers do impair judgment and thought processes enough to make activities such as driving hazardous and ill-advised.

Palliative Treatments for Pain Relief

Radiation therapy and surgery are often options for palliative treatment for pain resulting from cancer. These treatments reduce the size of tumors, relieving their pressure on surrounding tissues. The relief may extend months to years, depending on the cancer. There is no discomfort

associated with palliative radiation therapy. Palliative surgery does entail recovery from the surgery, though this typically follows a predictable and fairly rapid course after which relief from the cancer pain is often pronounced or complete.

Other Methods of Pain Management

Other methods that may help a person cope with pain include ACUPUNCTURE, BIOFEEDBACK, HYPNOSIS, YOGA, and MEDITATION. These methods incorporate MIND–BODY INTERACTIONS that provide physical, mental, and emotional changes to lessen the effects of pain. Acupuncture is also effective for relieving NAUSEA and other discomforts associated with CHEMOTHERAPY. These methods may be alternatives to medication that allow management of pain and return to normal activities.

See also CHRONIC PAIN; NEURON; TERMINAL PAIN.

R

radiation therapy The use of ionizing electromagnetic energy particles or waves to destroy cancer cells. Radiation is the emission of energy in a pattern of rays, such as visible light. Ionizing radiation is a form of energy of sufficient intensity to alter the electronic charge of atoms and the structure of molecules, such as ultraviolet light. At high exposure, such alteration changes the structures of cells. The effects of ionizing radiation on cellular structure can cause as well as treat cancer.

The substances that contain the ionizing energy particles are radioactive isotopes, also called radionuclides or radioisotopes, most of which occur in the natural environment though scientists can cultivate them in the laboratory for consistency and ready availability. As the radioisotope disintegrates it releases radiation at a known rate, which allows the radiation oncologist to determine the appropriate exposure times and frequencies.

RADIOISOTOPES USED IN RADIATION THERAPY

cesium-137 (^{137}Cs)	cobalt-60 (^{60}Co)
gold-198 (^{198}Au)	iodine-125 (^{125}I)
iodine-131 (^{131}I)	iridium-192 (^{192}Ir)
palladium-103 (^{103}Pd)	phosphorus-32 (^{32}P)
radium-226 (^{226}Ra)	yttrium-90 (^{90}Y)

The radiation oncologist determines which radioisotope or type of radiation to use based on the type of cancer, its location in the body, and how extensively the tumor has spread. Some types of radiation are more effective for penetration to tumors deep within the body and others are more effective for treating tumors close beneath the surface of the SKIN. How rapidly the radioisotope dissipates is important for internal radiation therapy in which the radiation oncologist implants radioactive pellets into the body to directly expose the cancer tumor to the radiation.

How Radiation Therapy Works to Treat Cancer

A key characteristic of cancer cells is that they divide rapidly and without much organization. Radiation therapy works by damaging the DNA within the cells, which prevents them from dividing. Though all cells in the body are vulnerable to such damage, radiation therapy selectively targets the tumor, limiting the exposure of healthy cells to the radiation. Because normal cells do not divide as rapidly as cancer cells and they divide in an organized process, they are able to recover from the radiation exposure. The exceptions are the cells of fast-growing tissues such as skin and HAIR, which may experience some damage as a result of radiation therapy. The radiation oncologist structures shields and blocks to protect healthy tissue from the radiation as much as possible.

A fundamental premise of radiation therapy is fractionation—dividing a lethal DOSE of radiation into numerous sublethal doses administered over a period time. The standard protocol for radiation therapy in the United States delivers the fractionated dosage of radiation daily five days a week for two to nine weeks. Depending on the cancer and the capabilities of the treatment facility, some radiation therapy protocols use radioisotopes and delivery methods that allow fewer doses administered over a shorter time and that vary the intensity of radiation according to the type and location of the cancer.

Types of Radiation Therapy

There are two basic types of radiation therapy, external beam and internal radiation. Some people receive both external beam and internal radiation therapy, depending on the type and location

of their cancer. In external beam radiation therapy, the source of radiation is outside the body, directed toward the tumor using a machine. The radiation oncologist determines the precise point at which the radiation needs to enter the body, called the treatment portal, and places small tattoo dots to mark its boundaries. These tattoos are permanent and serve as the template for aligning the radiation delivery path.

The machine that delivers the radiation therapy is either a linear accelerator (which is most common) or a cobalt machine. These are similar in appearance to a large X-RAY machine. When receiving radiation therapy the person lies on a table beneath the machine, often positioned with supports and blocks to maintain the proper alignment for the radiation to hit the tumor. Each treatment session may take 15 to 30 minutes, though the actual delivery of radiation takes only a few minutes.

Radiation therapy does not hurt or cause any discomfort, though the experience can be somewhat stressful for people who are claustrophobic (become uncomfortable in closed spaces) because the machine is very large and often very close during treatment. Because the source of the radiation is outside the body, the person receives only the directed energy and does not become radioactive. External radiation therapy is often among the treatments for LUNG CANCER, BREAST CANCER, PROSTATE CANCER, COLORECTAL CANCER, Hodgkin's lymphoma, THYROID CANCER, pharyngeal cancer, and some types of brain cancer.

INTRAOPERATIVE RADIATION THERAPY

Another form of external beam radiation therapy is intraoperative radiation, in which the person receives radiation to the surgical bed (site where the surgeon removed the tumor). Intraoperative radiation takes advantage of direct exposure to the site of the cancer to destroy any cancer cells that may have penetrated the tissue surrounding the tumor.

Internal radiation therapy, also called radiation seeding or brachytherapy, more directly targets the tumor with radioactive pellets (radioisotopes encased in thin wire containers) about the size of grains of rice, implanted in the body into or very near the tumor. Internal radiation therapy delivers a higher dose of radiation more directly to the tumor site, and often for a shorter duration, than would be possible with external beam radiation therapy. Internal radiation may be among the treatments for breast cancer, ENDOMETRIAL CANCER, thyroid cancer, CERVICAL CANCER, prostate cancer, and some cancers of the head and neck.

Internal radiation therapy may be

- interstitial, in which the radiation oncologist implants the radioactive pellets into the tumor or the tissue surrounding the tumor
- intracavitary, in which the radiation oncologist inserts the radioactive pellets into a natural body cavity such as the UTERUS or RECTUM
- intraluminal, in which the radiation oncologist inserts the radioactive pellets into a natural body passage such as the ESOPHAGUS or VAGINA

The implantation generally takes place with the person under general, regional, or local ANESTHESIA. After implantation the person is radioactive—that is, he or she emits ionizing radiation that can expose other people to its effects. Sometimes it is necessary to restrict contact with other people until the end of the course of treatment when the radioisotope dissipates enough to emit a level of ionizing radiation that is within safe limits. Sometimes the surgeon implants the pellets after an OPERATION to remove the tumor. An internal radiation implant remains in place for a few days to several weeks in most circumstances, though may remain for a few minutes to a few hours when the dose of radiation is very high and indefinitely when the optimal therapy is low-dose radiation over an extended time.

Risks, Side Effects, and Complications of Radiation Therapy

About half of people who have cancer receive radiation therapy during the course of their treatment. The general short-term side effects of radiation therapy include

- damage to the skin in the treatment area, similar to SUNBURN
- damage to hair follicles in the treatment area, resulting in local thinning or loss of hair

- mild NAUSEA
- tiredness and fatigue

Short-term side effects generally go away after the course of radiation therapy ends. Short-term risks, which are uncommon, include radiation BURNS to the skin and damage to tissues and organs in the treatment area that impairs their function. Long-term risks and complications of radiation therapy include destruction of the BONE MARROW, development of other types of cancer (notably LYMPHOMA and MULTIPLE MYELOMA), and permanent damage to tissues in the treatment area such as skin and MUSCLE. Specific types of radiation therapy have additional risks.

See also CANCER TREATMENT OPTIONS AND DECISIONS; CHEMOTHERAPY; SURGERY FOR CANCER.

recurrence Cancer that returns after treatment. The cancer may come back to its original site or appear in another part of the body. Recurrent cancer that spreads to multiple sites is metastatic. Treatment for recurrent cancer depends on the type of cancer, its location, and the treatment for the original cancer. Recurrent cancer occurs because cancer cells remain in the body after treatment and are able to reestablish themselves. Some cancers recur because their cells are particularly aggressive. Such cancers require increasingly aggressive treatment that may hold the cancer in check for periods of time, though these periods of REMISSION tend to become shorter and the cancer progresses. Other types of cancer persistently recur, such chronic lymphoma. Treatment can effectively manage such cancers for decades.

See also CELL STRUCTURE AND FUNCTION; METASTASIS.

remission The period of time during which a person in treatment for cancer is free from symptoms though the cancer may still be in the body. In complete remission all symptoms disappear; in partial remission some or most symptoms go away. Remission is generally the result, or may be the goal, of RADIATION THERAPY or CHEMOTHERAPY. Remission may last months to years, depending on the type of cancer. Alternating periods of remission and RECURRENCE (return of the cancer and its symptoms) characterize some cancers, such as chronic LYMPHOMA, chronic LEUKEMIA, KAPOSI'S SARCOMA, and SKIN CANCER.

See also METASTASIS.

S

sarcoma Cancer that arises from connective tissue such as BONE, TENDON, CARTILAGE, fat, MUSCLE, and other soft tissues. Sarcomas may also develop within the walls of BLOOD vessels, which contain connective tissue. Treatment generally combines surgery to remove the tumor with RADIATION THERAPY or, less commonly, CHEMOTHERAPY. Radiation exposure, such as occurs with radiation therapy for other cancers or with accidental or industrial exposure, increases the risk for sarcoma.

TYPES OF SARCOMA

Tumor	Location
chondrosarcoma	CARTILAGE
dermatofibrosarcoma	SKIN
fibrosarcoma	fibrous connective tissue (fibroblast proliferation)
hemangiosarcoma	BLOOD vessel
KAPOSI'S SARCOMA	connective tissue of skin, mucous membranes, organs
leiomyoma	smooth MUSCLE, such as the UTERUS
liposarcoma	fatty tissue
neurofibrosarcoma	nerves
osteosarcoma	BONE
synovial sarcoma	synovial membrane of a JOINT

See also ADENOCARCINOMA; BLASTOMA; CARCINOMA; LIPOMA; NEUROFIBROMATOSIS; SURGERY FOR CANCER.

screening for cancer See CANCER PREVENTION.

sentinel lymph node dissection Surgery to remove and biopsy the first LYMPH NODE in the LYMPH network that drains lymph from the location of a cancerous tumor. The sentinel node is important in determining the course of treatment for the cancer because it would be the first lymph structure to which cancer cells would migrate in METASTASIS. During the OPERATION to remove the tumor, the surgeon injects a dye into the tissues at the tumor's location. The first lymph node to show the presence of the dye is the sentinel node, which the surgeon then removes. If cancer cells are in the sentinel node, then the surgeon removes additional lymph nodes and possibly more tissue surrounding the tumor. If there are no cancer cells in the sentinel node, then the surgeon does not need to remove any further tissue. Sentinel lymph node dissection is increasingly common in surgery for BREAST CANCER, malignant melanoma, and other cancers that may remain localized.

See also LYMPHEDEMA; STAGING AND GRADING OF CANCER; SURGERY FOR CANCER.

signs and symptoms of cancer Though each type of cancer has specific signs and symptoms, some symptoms are universal to nearly all types of cancer. Such symptoms include

- unintended weight loss, often rapid
- general sense of not feeling well (malaise)
- fatigue that does not improve with sleep and rest
- unexplained FEVER or night sweats
- swollen though painless LYMPH nodes
- unexplained loss of APPETITE

Early symptoms are general and may indicate numerous health conditions other than cancer. However, early detection and diagnosis of cancer presents the best opportunity for successful treatment. Possible cancer symptoms in combination with risk factors such as age over 50 years, cigarette smoking, or OBESITY are more suspicious.

Specific symptoms of certain cancers that are worthy of a doctor's assessment include

- prolonged COUGH, which may suggest laryngeal cancer or LUNG CANCER
- a wound or sore that does not heal, which may suggest SKIN CANCER
- a change in bowel habits or rectal bleeding, which may suggest COLORECTAL CANCER
- a lump in the BREAST or testicle, which may suggest BREAST CANCER or TESTICULAR CANCER
- extended NAUSEA, VOMITING, or DIARRHEA may suggest ESOPHAGEAL CANCER, STOMACH CANCER, PANCREATIC CANCER, or colorectal cancer

See also BREAST SELF-EXAMINATION; CANCER PREVENTION; DIAGNOSING CANCER; LYMPH NODE; TESTICULAR SELF-EXAMINATION.

smoking and cancer Cigarette smoking is the leading cause of numerous types of cancer. Cigarette smoke contains more than 4,000 chemicals, none of which is beneficial to health and about 60 of which are known carcinogens (cancer-causing substances). Among the key carcinogens in cigarette smoke are formaldehyde, aromatic amines, arsenic, chromium, phenols, tar, and vinyl chloride.

Though LUNG CANCER is currently the leading cause of death from cancer in the United States, health experts believe it is also the most preventable cancer because of smoking's role in its development. Cigarette smoking accounts for 85 percent of the 172,500 people in whom doctors diagnose lung cancer each year. It also accounts for significant percentages of BREAST CANCER, BLADDER CANCER, PROSTATE CANCER, STOMACH CANCER, PANCREATIC CANCER, ENDOMETRIAL CANCER (cancer of the UTERUS), ESOPHAGEAL CANCER, oral cancer (cancer of the MOUTH and lips), laryngeal cancer (cancer of the THROAT), and acute myeloid LEUKEMIA (AML).

Cigarette smoking continues to decline among Americans, with only one in four men and one in five women now being regular smokers. Half of all Americans who ever smoked now no longer smoke. Health experts anticipate a corresponding decline in smoking-related cancers over the coming decades.

See also ANTISMOKING EFFORTS; CANCER PREVENTION; SMOKING AND CARDIOVASCULAR DISEASE (CVD); SMOKING CESSATION; SMOKING AND HEALTH.

staging and grading of cancer The standardized processes and guidelines for assessing the severity of cancer after diagnosis. A cancer's stage and grade help determine the most effective treatment options. Though each type of cancer has its own specific staging and grading protocol, general methodologies apply to nearly all types of cancer, except LEUKEMIA.

Cancer Staging

The stage of a cancer identifies how contained or widespread the cancer is. The traditional method of staging assigns a number to the level of the cancer's severity based on the tumor's location, penetration into lymph nodes, and spread to adjacent or distant tissues. The higher the number, the more extensive the cancer. A stage 0 cancer is small and completely contained, often in situ (confined to the cells in which the cancer started). A stage 4 cancer is widespread with multiple tumors distant from the primary tumor (site where the cancer first started). Staging criteria vary somewhat among the different types of cancer.

GENERAL CANCER STAGING: TRADITIONAL METHOD

Stage	Extent of Cancer
Stage 0	in situ; tumor confined to the cells of its origin
Stage 1	tumor remains localized though has spread beyond the cells of its origin
Stage 2	tumor has spread to adjacent tissues *or* lymph nodes
Stage 3	tumor has spread to adjacent tissues *and* lymph nodes or is locally recurrent
Stage 4	multiple tumors distant from the primary tumor; cancer is recurrent

Another method of tumor staging is the TNM system in which *T* represents the tumor size, *N* represents the involvement of local and regional lymph nodes, and *M* represents METASTASIS to distant sites. The TNM system is internationally standardized and provides more detail about the cancer's characteristics than the traditional, or stage grouping, method. It also allows for more precise characterization of the cancer. As is the

case with traditional staging, criteria vary somewhat among the different types of cancer.

GENERAL CANCER STAGING: TNM METHOD

Stage	Extent of Cancer
Tumor (T)	
T0	no evidence of cancer
Tis	in situ; tumor confined to cells of origin
T1	localized tumor less than 3 centimeters (cm) in size
T2	tumor is larger than 3 cm *or* has invaded adjacent tissues
T3	tumor is larger than 3 cm and has invaded adjacent tissues
T4	large tumor has invaded adjacent tissues or is inoperable
Lymph Nodes (N)	
N0	no cancer in regional lymph nodes
N1	cancer in local lymph nodes
N2	cancer in regional lymph nodes
N3	cancer in lymph nodes beyond the region of the primary tumor
Metastasis (M)	
M0	cancer remains local or regional (no METASTASIS)
M1	cancer has spread to distant sites (metastasis)

Cancer Grading

The grade of a cancer identifies the characteristics of its cells and their growth patterns. Grade is relevant only for cancers that can have varying aggressiveness, such as sarcomas and some types of brain cancer. The pathologist determines the tumor's grade from tissue samples and assigns a numeric value that indicates the tumor's aggressiveness and likelihood for metastasis. As with cancer staging, the criteria differ among the types of cancer, though in general a higher grade value indicates a more extensive or serious cancer. Some tumors have a mix of different cancer cells, in which case the pathologist usually assigns the higher grade to the tumor overall.

Stage, Grade, and Outlook

Oncologists use cancer staging and grading as the general framework for making treatment decisions and assessing prognosis (expected outcome). Though many types of cancer are treatable, controllable, or curable with today's range of treatment options, the individual variation in cancer diagnosis is significant. Each person who has cancer has a unique response based on numerous and sometimes intangible factors. Staging, grading, and other diagnostic parameters represent only a best attempt to characterize a cancer so as to structure an optimal treatment approach; they do not define the outcome.

See also CANCER TREATMENT OPTIONS AND DECISIONS; DIAGNOSING CANCER; LYMPH NODE; TUMOR MARKERS.

surgery for cancer An OPERATION to remove a cancerous tumor. Surgery is the first line of treatment for cancer that a surgeon can readily reach without endangering the person, and when there is a single defined tumor. Multiple tumors may also be appropriate for surgery, depending on the type of cancer, the location of the tumors, and how clearly contained the tumors are. Surgery is typically the primary therapy for treating cancer, with adjuvant (accompanying or follow-up) treatment with RADIATION THERAPY, CHEMOTHERAPY, IMMUNOTHERAPY, or HORMONE THERAPY for a comprehensive approach. A person might undergo chemotherapy or radiation therapy before surgery to shrink the tumor, and also may undergo such treatment after surgery to eradicate any remaining cancer cells.

How Surgery Works to Treat Cancer

Surgery may be therapeutic (attempt to remove the cancer) or palliative (remove enough of the tumor to relieve PAIN or other symptoms). As oncologic surgeons have learned more about how cancer grows and spreads in the body, surgery methods

GENERAL TUMOR GRADING

Grade	Cancer Cell Characteristics	Cancer Aggressiveness
G1	good differentiation, nearly normal cells	low
G2	moderate differentiation, somewhat abnormal cells	intermediate
G3	poor differentiation, abnormal cells	high
G4	no differentiation, unstructured cells	very high

have become more precise. As well, pathology analysis of the tumor has become more efficient and accurate. The surgeon sends samples of the tumor and surrounding tissue to the pathology laboratory during the operation for immediate examination by a pathologist. The pathologist's initial report helps the surgeon determine whether there is a need to remove additional tissue.

In therapeutic surgery the surgeon excises (cuts out) the tumor with a margin of healthy tissue to capture stray cancer cells at the tumor's edges. The goal of such surgery is to eliminate the cancer so the person makes a full recovery and remains cancer free (with or without adjuvant therapies). For large tumors that are difficult to remove, the surgeon may perform cytoreduction (also called tumor debulking) to reduce the size and presence of the cancer as much as possible with the goal of improving the effectiveness of other treatments such as chemotherapy or radiation therapy. In advanced cancer, inoperable tumors may create obstructions or grow into the space an organ ordinarily occupies. The surgeon may perform palliative surgery to remove enough of the tumor to relieve pressure on nerves, BLOOD vessels, and other structures that may be causing pain or interfering with an organ's function.

Types of Surgery

Until the 1990s the standard practice in therapeutic cancer surgery was to remove substantial tissue to ensure removal of the cancer, often resulting in radical surgery such as MASTECTOMY (removal of a BREAST to treat BREAST CANCER) or bowel resection (removal of the COLON to treat COLORECTAL CANCER). Improvements in the understanding of how cancer functions in the body in combination with advances in other treatments for cancer have shifted the approach in cancer surgery toward sparing tissue, organs, and limbs to preserve body structures and functions, relying on a combination of therapies to treat the cancer. When the stage and grade of cancer still requires radical surgery, advances in reconstructive surgery (often performed at the same time as the cancer surgery) have improved QUALITY OF LIFE after surgery.

MINIMALLY INVASIVE SURGERY may be an option for stage 0 cancers, which are small and narrowly confined to the site of origin. OPEN SURGERY is generally the preference for stage 1 and 2 cancers, so the surgeon is able to remove all of the cancer and obtain an acceptable margin of healthy tissue. The length of hospitalization and recovery from the surgery depends on the operation and the person's overall health status. Many people who undergo surgery as primary treatment for cancer are otherwise healthy and typically experience a prompt and uneventful course of recovery.

Risks, Side Effects, and Complications of Surgery to Treat Cancer

Though cancer surgery methods are very advanced, risks and complications are possible. Diagnostic imaging procedures provide the surgeon with a good understanding of where the cancer is and how it involves tissues and organs. However, the surgeon cannot know for certain the nature and extent of the tumor until the surgery exposes it for full examination. Though most surgeries go exactly as anticipated, unexpected findings can shift the operation in a different direction. The surgeon typically recognizes the potential for the unexpected and includes discussion of such possibilities in the informed consent process. It is important to talk with the surgeon the anticipated benefits and potential risks of the planned operation. A second opinion consultation with another surgeon or with a medical oncologist for a discussion of nonsurgical treatment options is often a good idea, particularly when the proposed surgery is extensive or complex.

See also CANCER TREATMENT OPTIONS AND DECISIONS; MOHS'S SURGERY; QUALITY OF LIFE; PLASTIC SURGERY; SURGERY BENEFIT AND RISK ASSESSMENT.

T

tumor markers Molecules, often proteins, cancer cells and some other cells produce. Tumor molecules appear in the BLOOD or in the URINE, which makes it possible to measure their concentrations. Elevated levels of certain tumor markers indicate the need for further evaluation to determine whether a cancer is present. However, most tumor markers are not in themselves conclusive for specific types of cancer, even though they may occur in certain cancers as they can occur in numerous benign (noncancerous) conditions. As well, different types of cancer may generate elevations in a particular tumor marker, so elevated concentrations of the marker do not provide information of specific diagnostic value. Oncologists must evaluate tumor marker levels in the context of other clinical findings. Because so many factors influence tumor markers, oncologists disagree as to their usefulness, especially for screening and diagnostic purposes.

Some tumor markers are more useful for monitoring the effectiveness of treatment, because the oncologist can track the fall and rise of the marker's level in the blood circulation. However, tumor markers may rise with successful CHEMOTHERAPY because the dying cancer cells release high quantities of proteins into the blood. After successful treatment, monitoring tumor marker levels may provide early evidence of RECURRENCE should it develop.

COMMON TUMOR MARKERS

Tumor Marker	Corresponding Cancer	Reliability
alpha-fetoprotein (AFP)	LIVER CANCER (hepatocellular cancer); some ovarian cancers; some testicular cancers	moderate for diagnosis
Bence Jones protein	MULTIPLE MYELOMA	effective for diagnosis effective for monitoring treatment
beta-2 microglobulin (B2M)	multiple myeloma; some lymphomas	questionable for diagnosis effective for monitoring treatment
bladder tumor antigen (BTA)	BLADDER CANCER	moderate for diagnosis effective for monitoring treatment
CA-27.29	BREAST CANCER	unreliable for diagnosis in early stages; moderate for diagnosis in metastatic disease effective for RECURRENCE elevation possible in women who do not have cancer

Tumor Marker	Corresponding Cancer	Reliability
CA-72-4	OVARIAN CANCER; STOMACH CANCER; PANCREATIC CANCER; COLORECTAL CANCER	unreliable for diagnosis
CA-125	ovarian cancer	unreliable for diagnosis may be elevated in women who have previously had cancer and are currently cancer free elevated in endometriosis and benign OVARIAN CYST
CA-5-3	breast cancer	unreliable for diagnosis in early stages; moderate for diagnosis in metastatic disease effective for recurrence elevation possible in women who do not have cancer
CA-9-9	pancreatic cancer	moderately reliable for diagnosis
CALCITONIN	medullary THYROID CANCER	effective for diagnosis
CARCINOEMBRYONIC ANTIGEN (CEA)	colorectal cancer; LUNG CANCER; breast cancer	unreliable for diagnosis effective for recurrence elevated in numerous noncancerous health conditions elevated in people who smoke
chromogranin A	neuroendocrine cancers	moderate for diagnosis
HER-2/neu	breast cancer	unreliable for diagnosis moderate for monitoring treatment
human chorionic gonadotropin (hCG)	gestational trophoblastic neoplasia (GTN); TESTICULAR CANCER; ovarian cancer	moderate for diagnosis effective for monitoring treatment
M-protein	multiple myeloma	effective for diagnosis effective for monitoring treatment
NEURON-specific enolase (NSE)	small-cell lung cancer (SCLC)	modest for diagnosis moderate for monitoring treatment
PROSTATE-SPECIFIC ANTIGEN (PSA)	prostate cancer	effective for diagnosis effective for monitoring treatment elevated in BENIGN PROSTATIC HYPERPLASIA (BPH)

See also CANCER PREVENTION; DIAGNOSING CANCER; ONCOGENES; TUMOR SUPPRESSOR GENES.

tumor suppressor genes Genes that stop cell growth, preventing tumor development. In health, tumor suppressor genes direct the production of proteins to block cell division when there are abnormalities in the cell, such as DNA damage. When mutated, tumor suppressor genes lose the ability to influence cell division. Cells may then proliferate without regulation, the foundation of cancer. MOLECULARLY TARGETED THERAPIES and MONOCLONAL ANTIBODIES (MABS) show significant promise for altering the function of mutated tumor suppressor genes to restore their ability to block cell growth.

IDENTIFIED TUMOR SUPPRESSOR GENES

Gene	Cancer Connection
APC	COLORECTAL CANCER
BRCA-1/BRCA-2	BREAST CANCER, OVARIAN CANCER
MEN-1/MEN-2	MULTIPLE ENDOCRINE NEOPLASIA (MEN)
NF1/NF2	NEUROFIBROMATOSIS
PTEN	THYROID CANCER
Rb	RETINOBLASTOMA, osteosarcoma, breast cancer, LUNG CANCER
TP53 (p53)	lung cancer, breast cancer, LIVER CANCER, CERVICAL CANCER, SKIN CANCER, PROSTATE CANCER, ovarian cancer
WT1	WILMS'S TUMOR

See also CELL STRUCTURE AND FUNCTION; GENE; ONCOGENES.

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