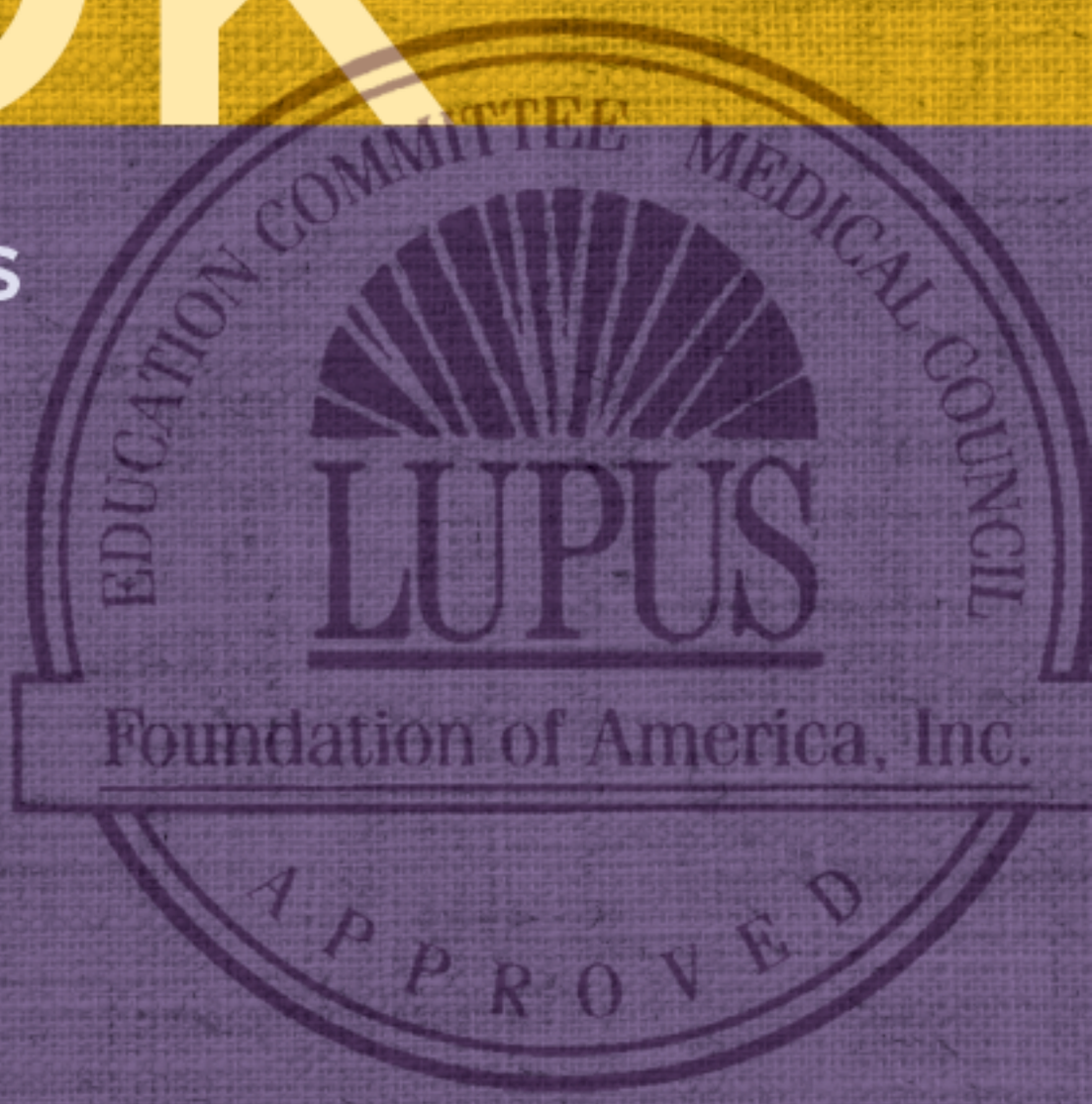
SIXTH EDITION

THE LUPUS BOOK

A Guide for Patients and Their Families



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A Guide for Patients and Their Families

Sixth Edition

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Oxford University Press is a department of the University of Oxford. It furthers the University's objective of excellence in research, scholarship, and education by publishing worldwide. Oxford is a registered trade mark of Oxford University Press in the UK and certain other countries.

Published in the United States of America by Oxford University Press
198 Madison Avenue, New York, NY 10016, United States of America.

First Edition published in 1995
Second Edition published in 2000
Third Edition published in 2005
Fourth Edition published in 2009
Fifth Edition published in 2012

Library of Congress Cataloging-in-Publication Data
Names: Wallace, Daniel J. (Daniel Jeffrey), 1949- author.
Title: The lupus book : a guide for patients and
their families / Daniel J. Wallace, MD.
Description: Sixth edition. | New York, NY : Oxford University Press, [2019] |
Includes bibliographical references and index.
Identifiers: LCCN 2018036152 | ISBN 9780190876203
Subjects: LCSH: Systemic lupus erythematosus—Popular works.
Classification: LCC RC924.5.L85 W35 2019 | DDC 616.7/72—dc23
LC record available at https://lccn.loc.gov/2018036152

1 3 5 7 9 8 6 4 2

Printed by Sheridan Books, Inc., United States of America

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Preface to the Sixth Edition

I am amazed at the number of lupus patients referred to me who have received only a cursory explanation of their disease and a brief discussion of its management. They have no idea what to expect and therefore usually have many questions, some of which I cannot yet answer. I have written this book for them, their caregivers, and their physicians.

The Lupus Book has sold nearly 200,000 copies since it was first published in 1995. The sixth edition adds numerous tables, extensively revises basic science and research sections, and adds sections on new emerging areas such as the microbiome, lupus clinical trials, and developing therapies. Over 500 changes have been made in the text since the previous edition. For those interested in additional resources, a "Further Reading" listing has been added for each chapter.

I hope you find this work informative and enjoyable to read. If you are reading this book, you may have been diagnosed with lupus or suspect that you have it. It is my hope that this book will help you work with your physician. In some instances, to flesh out the details, I have used composite cases based on real people I treat. Of course—as I learned early in my practice—no two patients have exactly the same experience with the disease. But some of the patients' personal stories may ring true and help you cope with your own symptoms.

This book is not intended to be a substitute for advice given by your family physician or the specialist you have been referred to. These doctors know your medical history and related problems far better than I ever will and can provide you with a perspective that is not possible for me to impart.

The Lupus Book is not meant to be read from front to back. It is intended to be a resource for patients and caregivers who are interested in how various aspects are approached in particular. Chapters 5 through 9 may be very technical. The reader should not get discouraged; understanding immunology is a daunting task, even for physicians.

As a physician who specializes in rheumatology and has a special interest in lupus, I have tried to anticipate your questions with the most up-to-date information we now have on causes, prevention, cure, exercise, diet, and many other

important topics. This book is a distillation of my experience in treating over several thousand lupus patients. It is aimed at patients and allied health professionals (e.g., physical therapists, nurses, occupational therapists, social workers, psychologists, and others) who may be involved in the care of lupus patients.

I am indebted to my wife and our three children (Phil, Sarah, and Naomi) and amazing grandchildren for my imposition on their time in preparing this book, as well as my research and administrative staff (especially Jody Stanley and Jennifer Nelson) for their patience and support.

Part I
INTRODUCTION AND DEFINITIONS

Where should we start? The most logical place is with a definition of lupus. We look at how it is classified as a disease and place it in its proper historical perspective. This is followed by an overview of how lupus is distributed in the population—in other words, who gets the disease, which parts of the world have the highest prevalence of lupus, how many people have lupus in the United States and at what age, and which sex is most affected.

1
Why Write a Book on Lupus?

The first time someone hears the words "lupus erythematosus," he or she usually says, "What?" When I first started my practice, patients identified the term with Peter Lupus, one of the characters on *Mission Impossible*, a popular television series (antedating the movies) in the late 1960s. Sometimes it looks as though finding a cure for lupus is an impossible mission, but there is much we do know, and the aim of this book is to share that knowledge.

Lupus is the common name for the disorder known technically as lupus erythematosus. This formal name includes systemic lupus erythematosus—where *systemic* means affecting the entire body or internal system—or SLE for short. Although underrecognized, lupus is an extremely important disease for many reasons:

- *In the United States, nearly 1 million people suffer from lupu*s related disorders (put in italics). It is more common than better-known disorders such as leukemia, multiple sclerosis, cystic fibrosis, and muscular dystrophy combined. Those who develop SLE do so in the prime of life. Ninety percent of these sufferers are women, 90 percent of whom are in their childbearing years. Moreover, the effects of the disease disrupt family life and account for billions of dollars in lost work productivity.
- *Understanding the immunology of lupus will help us better understand HIV, infections in general, allergies, and cancer*. Medical students are often told, "Know lupus and you know medicine," and lupus is the paradigm of autoimmunity. This is because SLE can affect every part of the body. The basic immunopathology of lupus, or the factors that cause the disease, get to the core of how the human immune system functions. Nearly every major advance in understanding lupus immunology has had a spillover effect—it has helped not only SLE patients but also those with immune-related disorders such as HIV, other infectious processes, allergies, and cancer.
- *Lupus can be a very difficult disease to diagnose*. Many lupus patients look perfectly healthy, but surveys have shown that newly diagnosed patients have had symptoms or signs for an average of 3 years. A young woman who

complains of fatigue, achiness, stiffness, and low-grade fevers or swollen glands is often told she is experiencing stress, has picked up a virus that is going around, or—worse—that she is exaggerating her symptoms. By the time she is diagnosed with SLE, permanent damage to vital organs such as the lungs or kidneys may have occurred. (Advanced lupus is usually easy to diagnose.) This book attempts to increase public awareness of the disease, which could lead to earlier diagnosis.

- *There is a shortage of doctors capable of diagnosing and treating SLE, a disease studied and managed by rheumatologists*. Rheumatology is one of the recognized subspecialties of internal medicine, along with cardiology, gastroenterology, and pulmonary medicine, a field in which only 1 percent of physicians in the United States are certified to practice. The American College of Rheumatology (ACR) has estimated that the United States will be short nearly 3,000 rheumatologists by 2030. Only 4,000 rheumatologists are in active private full-time practice as of this writing.
- *Many patients who are told they have SLE do not*. Some 10 million Americans have a positive lupus blood screen (called antinuclear antibody, or ANA), but only about 1 million of these actually have SLE or lupus-related disorders. Since normal patients and healthy relatives of those with autoimmune disease can have positive tests for lupus, some physicians take the test results at face value and inform their patients (especially young women) that they do indeed have the disease or may succumb to it in the future. Such patients may suffer ill effects, especially if unnecessary treatments are prescribed. Also, many disorders mimic SLE. A positive blood test for lupus may be found during a viral illness, and unsuspecting physicians may draw the wrong conclusions. Disorders closely related to SLE such as scleroderma or polymyositis (see the glossary for definitions of technical terms) may exhibit similar test results but are treated quite differently. In discerning among these conditions, a complex diagnostic workup is often necessary, and few physicians are equipped to interpret the necessary battery of tests. In these instances, most physicians will consult a board-certified rheumatologist or recommend that their patients visit such a specialist.

Now let's get started. We'll begin by discussing what lupus really is.

FURTHER READING

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2. Al Daabil M, Massarotti EM, Fine A, et al. Development of SLE among "potential SLE" patients seen in consultation: long-term follow-up. *Int J Clin Pract.* 2014;68(12):1508–1513.

2
What Is Lupus?

In simple terms, lupus erythematosus develops when the body becomes allergic to itself. Immunologically speaking, it is the opposite of what takes place in cancer or HIV. In lupus, the body overreacts to an unknown stimulus and makes too many antibodies, or proteins directed against body tissue. Thus, lupus is called an *autoimmune disease* (*auto* meaning *self*).

IS THERE AN "OFFICIAL" DEFINITION OF LUPUS?

The American College of Rheumatology (ACR), a professional association to which nearly all rheumatologists in the United States belong, devised criteria for clinical trials and population studies rather than for diagnostic purposes in 1971. These criteria were revised in 1982 and 1997, and they are shown in Table 2.1. The presence of 4 of the 11 criteria confirms the diagnosis. These criteria apply only to systemic lupus erythematosus (SLE) and not to drug-induced or discoid (cutaneous) lupus. (These various forms of lupus are discussed in the section What Types of Lupus Are There?)

The first four criteria concern the skin: sun sensitivity, mouth sores, butterfly rashes, and discoid lesions (sores resembling a disk).

The second four criteria are associated with specific organ areas: the lining of the heart or lung, the kidneys, the central nervous system, and the joints.

The remaining three criteria specify relevant laboratory abnormalities: altered blood counts (low red blood cells, white blood cells, or platelets), positive antinuclear antibody (ANA) testing, and other blood antibody abnormalities of the disease. The ANA test is used as the primary diagnostic tool to determine whether a person has lupus, but there are limits to its reliability, which we discuss in Chapter 6. A patient can have SLE without fulfilling ACR criteria. For example, a patient with a positive kidney biopsy for lupus may meet only two criteria if the ANA is also positive. Though they are over 90 percent sensitive and specific for the diagnosis of SLE, the ACR criteria are primarily used for research purposes as entry criteria for a study.

Table 2.1. *American College of Rheumatology (1997) Revised Criteria for the Classification of Systemic Lupus Erythematosus (SLE)*

A person is said to have SLE if 4 of the following 11 criteria are present at any time:

Skin criteria

1. Butterfly rash (lupus rash over the cheeks and nose)
2. Discoid rash (a thick, disk-like rash that scars, usually on sun-exposed areas)
3. Sun sensitivity (rash after being exposed to ultraviolet A and B light)
4. Oral ulcerations (recurrent sores in the mouth or nose)

Systemic criteria

5. Arthritis (inflammation of two peripheral joints with tenderness, swelling, or fluid)
6. Serositis (inflammation of the lining of the pleura [lung] or the pericardium [heart])
7. Kidney disorder (protein in urine samples or abnormal sediment in urine seen under the microscope)
8. Neurologic disorder (seizures or psychosis with no other explanation)

Laboratory criteria

9. Blood abnormalities (hemolytic anemia, low white blood cell counts, low platelet counts)
10. Immunologic disorder (blood testing indicating either antiphospholipid antibodies, lupus anticoagulant, anti-DNA, false-positive syphilis test, or a positive anti-Smith antibody [anti-Sm])
11. Positive antinuclear antibody blood test

Many other manifestations of SLE are not included in the ACR criteria. They are excluded because they are not *statistically* important in differentiating SLE from other rheumatic diseases. For example, a condition known as Raynaud's phenomenon (when one's fingers turn white and then blue in cold weather) is present in one third of lupus patients. But it is not included in the criteria because 95 percent of those suffering from scleroderma also have Raynaud's. In other words, Raynaud's is not specific to SLE and therefore does not provide enough proof to classify someone as having SLE. In 2012, the Systemic Lupus International Collaborative Clinics (SLICC) proposed a classification for SLE that takes into account recent advances. It is as sensitive and specific as the ACR criteria, but it allows patients to be diagnosed with SLE who have a positive biopsy, additional laboratory tests, and neurologic findings. See Table 2.2. A committee of the ACR and the European League Against Rheumatism (EULAR) is currently working on an international criteria set based on an updated means of ascertainment known as the Delphi method that has proven successful for other rheumatic diseases. The preliminary criteria are shown in Table 2.3.

These particular manifestations of SLE will be covered in detail in later chapters.

WHAT TYPES OF LUPUS ARE THERE?

Sometimes the autoimmune reaction of lupus can be limited just to the skin and may result in a negative ANA blood test. This condition is called *cutaneous* or *discoid lupus erythematosus* (DLE). Though DLE is not an entirely accurate term

Table 2.2. *Systemic Lupus Erythematosus International Collaborative Clinics (SLICC) Classification for Systemic Lupus Erythematosus*

I. Biopsy documented nephritis excluding other causes *or*
II. One clinical and one immunologic criterion from the following:
  A. Clinical criteria in the absence of other causes
    1. Acute cutaneous rash (malar, sun sensitive, maculopapular, toxic epidermal necrolysis variant)
    2. Chronic cutaneous lupus (discoid, hypertrophic, profundus, tumidus, chilblains, mucosal, lichenoid)
    3. Oral ulcers (buccal, tongue, or nasal)
    4. Nonscarring alopecia
    5. Nonerosive inflammatory arthritis
    6. Serositis (pleural, pericardial)
    7. >0.5 G/day equivalent proteinuria or red blood cell urinary casts
    8. Neurologic (seizures, psychosis, mononeuritis multiplex, myelitis, peripheral/cranial neuropathy, acute confusional state)
    9. Hemolytic anemia
    10. Leukopenia (<4 K) or lymphopenia (<1 K)
    11. Thrombocytopenia (<100 K)
  B. Immunologic criteria
    1. Antinuclear antibody present above reference range
    2. Anti-double-stranded DNA >2 times reference range
    3. Antiphospholipid antibody (lupus anticoagulant, false-positive syphilis serology, anticardiolipin antibody greater than twice normal range, or anti-beta-2 glycoprotein)
    4. Anti-Sm
    5. Low C3, C4, or CH50 (total hemolytic complement)
    6. Positive direct Coombs without hemolytic anemia

From Petri M, Orbai AM, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematous. *Arthritis Rheum.* 2012;64(8):2677–2686.

(see Chapter 12), it helps distinguish these patients from those suffering with systemic lupus. About 40% of lupus patients exhibit this condition. When internal features are also present and fulfil criteria, we describe the condition as SLE.

SLE patients who have symptoms of achiness, fatigue, pain on taking a deep breath, fever, swollen glands, and signs of swollen joints or rashes but whose internal organs are not involved (e.g., the heart, lungs, kidneys, or liver) are said to have *non-organ-threatening disease*. Statistics vary, but on the basis of my own clinical experience, I estimate that about 25 percent of all lupus patients fall into this category. Patients with non-organ-threatening disease have a normal life expectancy, and it is uncommon for them to develop disease in the major organs after the first 5 years of having the disease.

On the other hand, involvement of the heart, lungs, or kidneys, or the presence of liver or serious blood abnormalities indicates that an *organ-threatening disease* is at work. This may become life-threatening if the patient is not treated with corticosteroids or other interventions. Another 25 percent of all lupus patients fall into this category.

Table 2.3. *Proposed ACR/EULAR classification criteria: ANA ≥ 1:80 and score ≥ 10 points across 22 domains*

Clinical Domain	*Criteria*	*Weight*
Constitutional domain	Fever	2
Cutaneous domain	Non scarring alopecia	2
	Oral ulcers	2
	Subacute cutaneous or discoid lupus	4
	Acute cutanous lupus	6
Arthritis domain	Synovitis >=2 joints or tenderness >=2 joints and >=30 minutes of morning stiffness	6
Neurological domain	Delirium	2
	Psychosis	3
	Seizure	5
Serositis domain	Pleural of pericardial effusion	5
	Acute pericarditis	6
Hematological domain	Leukopenia	3
	Thrombocytopenia	4
	Autoimmune hemolysis	4
Renal domain	Proteinuria > 0.5g/24 hours	4
	Class II or V Lupus nephritis	8
	Class III or IV Lupus nephritis	10
	Immunological domain	
Antiphospholipid antibody domain	Anti-Cardiolipin IgG or Anti-Beta2 GP IgG or Lupus anticoagulant	2
Complement Protein domain	Low C3 or Low C4	3
	Low C3 and Low C4	4
SLE specific antibody domain	Anti-dsDNA	6
	Anti-Smith	6

Aringer M et al. *Annals of the Rheumatic Diseases* 2018;77:60.

Some patients with lupus develop the disease for the first time from a prescription drug and have what is termed *drug-induced lupus erythematosus*. The drug-induced form is usually less severe than SLE and usually disappears after the patient stops taking the particular drug. Occasionally, however, short courses of lupus medication are required for these patients.

Perhaps 5 to 10 percent of the individuals who fulfill the ACR criteria for SLE may also fulfill the ACR criteria for another autoimmune disorder such as scleroderma (tight skin with arthritis), dermato-/polymyositis (inflammation of the muscles), or rheumatoid arthritis (a potentially deforming joint inflammation). These patients are said to have *mixed connective tissue disease* (MCTD) if they possess a particular autoantibody (anti-RNP). If they do not, the patients are said to have a *crossover* or *overlap syndrome*. This classification system is summarized in Table 2.4. A group of patients who have lupus-associated symptoms, signs, or laboratory abnormalities but do not fulfill ACR criteria

Table 2.4. *Types of Lupus Erythematosus*

Cutaneous (discoid) lupus erythematosus (40%)
Systemic lupus erythematosus (50%)
Non-organ-threatening disease (25%)
Organ-threatening disease (25%)
Drug-induced lupus erythematosus (<1%)
Crossover or overlap syndrome and/or mixed connective tissue disease (10%)
Neonatal lupus (<1%)

for any rheumatic disorders have an *undifferentiated connective tissue disease* (UCTD), which is reviewed in Chapter 23.

Finally, the presence of a lupus rash at birth or congenital heart block with a positive SSA (Ro) antibody is termed *neonatal lupus*. Several hundred cases have been reported in the United States.

WHAT'S IN STORE FOR THE READER

Don't be overwhelmed by all these facts and figures. This chapter has simply provided you with an overview of the book, and all the points mentioned will be discussed again in more detail in later chapters.

We close this first part with a brief historical background and an overview about who gets lupus (Chapters 3 and 4). In Parts II and III, the heart of the book, we look at the immune system and how it relates to SLE (Chapters 5–9). We discuss the manifestation of the disease in different areas of the body, such as the joints, the gastrointestinal system, the kidneys, and other organs (Chapters 12–20), and talk about the role of blood testing (Chapter 11). We will review the necessary clinical and diagnostic studies (X-rays, scans, etc.) that are used in assessing lupus (Chapters 12–20), as well as problems unique to specific circumstances, such as pregnancy, infection, and lupus in children and the elderly (Chapters 22, 23, 29, and 30). Next, we take up the treatment of lupus—the physical measures we can take to combat the disease, the various medications, and the emotional support a patient will need from his or her family and physician (Chapters 24–28). Finally, future directions and advances soon to take place are detailed in Chapters 32 and 33.

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3
The History of Lupus

Lupus is the Latin word for *wolf*, and it is common medical lore that the "butterfly rash" seen on the cheeks of many lupus patients is so similar to the facial markings of a wolf that our ancestors chose the name for this reason. The technical name for the disease we know of as lupus—*lupus erythematosus*—was first applied to a skin disorder by a Frenchman, Pierre Cazenave, in 1851, though descriptive articles detailing the condition date back to Hippocrates in ancient Greece (Figure 3.1).

Accurate treatises on the skin disorders associated with lupus were published in the mid-1800s by the great Viennese physicians Ferdinand von Hebra and his son-in-law Moriz Kaposi (for whom Kaposi's sarcoma is named). The first suggestions that the disease could be internal (more than skin deep and affecting the organs of the body) appeared in these writings. However, it was Sir William Osler (the founder of our first real medical internship and residency programs in the 1890s at Johns Hopkins) who wrote the earliest complete treatises on lupus erythematosus between 1895 and 1903. In addition to describing such symptoms as fevers and aching, he clearly showed that the central nervous, musculoskeletal, pulmonary, and cardiac systems could be part of the disease.

The golden age of pathology in the 1920s and 1930s led to the first detailed pathologic descriptions of lupus and showed how it affected kidney, heart, and lung tissues. Early discussions of abnormal blood findings such as anemia (low red blood cell count or low hemoglobin) and low platelet count (cells that clot blood) appeared during this time. We had to wait until 1941 for the next breakthrough, which took place at Mount Sinai Hospital in New York City. There, Dr. Paul Klemperer and his colleagues coined the term "collagen disease" on the basis of their clinical research. Although this term is a misnomer (collagen tissues are not necessarily involved in lupus), the evolution of this line of thinking led to our contemporary classification of lupus as an "autoimmune disorder," based on the presence of antinuclear antibody (ANA) and other autoantibodies.

The first arthritis unit with a special interest in lupus was started by Marian Ropes at the Massachusetts General Hospital in Boston in 1922. In those days, no blood test to diagnose lupus was available. In fact, until 1948 there were no

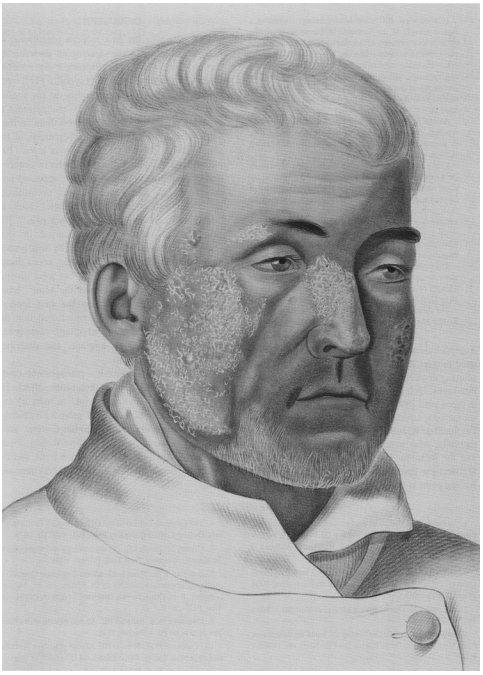

Figure 3.1. *A Patient with Lupus from Pierre Cazenave's Monograph, 1846*

effective treatments for lupus except for local skin salves or aspirin. Dr. Ropes observed that half of her patients got better and half of them died during the first 2 years of treatment. Indirectly, she was classifying her patients into "organ-threatening" and "non-organ-threatening" categories, but in many cases she had no way short of a tissue biopsy to determine to which subset a patient belonged.

In 1946, a Mayo Clinic pathologist named Malcolm Hargraves performed a bone marrow examination on a patient and absentmindedly kept a tube from the procedure in his pocket for several days. In a bone marrow examination, the physician removes a tissue sample from bone (usually from the sternum or pelvis, where blood components are made). After finally retrieving the tube, Hargraves observed a unique cell on his microscope slides, which became known as the LE cell. Published in 1948, his description of the LE, or lupus erythematosus, cell was one of the landmark developments in the history of rheumatology. This cell was representative of the systemic inflammatory process; its identification allowed doctors for the first time to diagnose the disease faster and more reliably. Dr. Hargraves and others were quick to show how LE cells could be looked for in peripheral blood samples and found that 70 to 80 percent of patients with active systematic lupus erythematosus (SLE) possessed these cells. At long last, patients with the disease could be readily identified. Researchers were on a roll: in the following year, 1949, another landmark event took place. Dr. Phillip Hench, another

Mayo Clinic physician and one of two rheumatologists ever to win the Nobel Prize in Medicine, demonstrated that a newly discovered hormone known as cortisone could treat rheumatoid arthritis. This hormone was administered to SLE patients throughout the country, and immediately dramatic life-saving took place.

The final chapter of our story evolved during the 1950s, when the concept of autoimmune disease was formalized and the LE cell was shown to be part of an ANA reaction. This led to the development of other tests for autoantibodies, which enabled researchers to characterize the disease in a more detailed and definitive manner. My mentor, Dr. Edmund Dubois, amassed an incredible 1,000 patients with lupus at the Los Angeles County/University of Southern California School of Medicine and in his private practice based at Cedars-Sinai Medical Center and was among the first researchers to explore the natural course of the disease and advise how best to treat it. Also during this time, cancer chemotherapy agents such as nitrogen mustard were shown to be effective in the management of serious organ-threatening complications of SLE when used together with corticosteroids. In 2011, the first new drug approved for lupus by the Food and Drug Administration, belimumab, came on the market. This occasion marked the advent of "targeted" or "biologic therapies" and ushered in a new age of lupus management.

With this historical context in mind, we now turn our attention to the present and a discussion of who gets lupus and why.

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4
Who Gets Lupus?

If we include thyroiditis, 3 to 5 percent of Americans develop an autoimmune disease in their lifetime. How many lupus patients are there in the United States? It is not as easy to answer this question as it might seem. In the 1990s, the National Arthritis Data Workshop estimated that there were 239,000 Americans with systemic lupus erythematosus (SLE). These numbers, however, do not include those patients who have discoid lupus or drug-induced lupus. However, based on patients being told that they had lupus by at least one doctor, a Lupus Foundation of America survey suggested that the prevalence of SLE could be as high as 2 million in the United States. This has led to misleading assumptions about the true number of people with SLE in the United States. The *incidence* of a disease is defined as the number of new cases per time period (e.g., year), whereas *prevalence* denotes the number of sufferers in the population.

In 2004, the Centers for Disease Control (CDC) funded the creation of national lupus registries in parts of Georgia, Michigan, Manhattan, and northern California. They utilized a methodology that collected reports of lupus from hospitals and discharge diagnoses, integrated health care systems, the US Renal Data System, pharmacy records, and commercial laboratories. The diagnosis of lupus was validated by a consensus panel of rheumatologists to assure they fulfilled either the ACR criteria or had a positive renal biopsy. The findings were published between 2014 and 2017 in multiple publications. In all, a population of 6.4 million was surveyed. The CDC found that the incidence and prevalence were remarkably similar in all regions: 64/100,000 individuals had lupus, or roughly 1 case per 1,500 people. Women had a nine- to tenfold increased risk compared to men, and blacks and Native Americans had a three- to fourfold risk for developing the disease. Hispanics and Asians had greater risk and were between the black and white population. Hence, there are approximately 250,000 people in the United States fulfilling the accepted criteria not counting those who clearly have the disease but do not meet the criteria, which are only 90 percent accurate. See Table 4.1.

Chronic cutaneous (mostly discoid) is three times more common in women than men with a prevalence of 30 per 100,000 individuals. The actual number

Table 4.1. *Who Gets Lupus?*

1. There are probably 300,000 cases of true SLE in the United States.
2. The risk for developing SLE is threefold in African Americans and Native Americans, ninefold in females versus males, and probably doubled in US Asians and Hispanics.
3. One in 1,500 people in the United States have SLE, including 1 in 250 African American women and 1 in10,000 white males.
4. There are probably 1,000 children born each year with neonatal lupus in the United States.
5. 17,000 of the 300,000 with SLE were diagnosed lupus before the age of 18.
6. There are probably 300,000 cases of cutaneous lupus (without SLE) in the United States.
7. 10,000 cases of drug induced lupus are diagnosed annually in the United States. It resolves within months in 95%.
8. The prevalence of lupus throughout the world is greatest in South America and Asia and the least in Europe.

approaches the same number as SLE since these patients often do not often seek medical attention (other than dermatology) and are rarely hospitalized. The prevalence of children under the age of 18 developing lupus is 6 per 100,000 people, or 1 case per 17,000. There are probably seven cases of undifferentiated connective tissue disease for every patient with lupus.

International surveys have come to similar conclusions. The prevalence of lupus in the Caribbean is 48/100,000, Mexico 60/100,000, South America 98/100,000, Asia 59/100,000, and Europe 20/100,000 in work published since 2000.

AGE OF ONSET

Lupus has been recorded in individuals at birth (*neonatal lupus*) and has been diagnosed in some people as old as 89. Nevertheless, 80 percent of those afflicted with SLE develop it between the ages of 15 and 45. Neonatal lupus is limited to children of mothers who carry a specific autoantibody (an antibody that reacts against the body's own tissues) called the anti-Ro (or SSA) antibody, which will be discussed in Chapter 30. This is one of the autoantibodies that crosses the placenta. For example, the skin rash of neonatal lupus is a self-limited process that disappears during the first year of life because the mother's antibody gets "used up" and the baby cannot make more of it. Children may develop SLE between the age of 3 years and the onset of puberty. This form of lupus is usually a severe, organ-threatening disease but fortunately accounts for less than 5 percent of all lupus cases. The onset of lupus after age 45 or after menopause is uncommon, and a diagnosis of lupus past the age of 70 is extremely unusual. Late-onset lupus infrequently threatens organ systems, and it can be mistaken for rheumatoid arthritis, Sjögren's syndrome, or polymyalgia rheumatica (see Chapters 22 and 23 for a discussion of these conditions).

Table 4.2. *Sex Ratios of Onset or at First Diagnosis of Systemic Lupus Erythematosus*

Age (Years)	*Female-to-Male Ratio*
0–4	1.4:1
5–9	2.3:1
10–14	5.8:1
15–19	5.4:1
20–29	7.5:1
30–39	8.1:1
40–49	5.2:1
50–59	3.9:1
60–69	2.2:1

SEX OF SLE PATIENTS AND TRENDS

In children and in adults over the age of 50, the incidence of lupus demonstrates only a slight female predominance; however, between the ages of 15 and 45, close to 90 percent of diagnosed patients are women. The reasons for this are discussed in Chapter 17. Overall, 80 to 92 percent of all Americans with SLE are women. The percentages are less for discoid lupus, where 70 to 80 percent are women, and for drug-induced lupus, which occurs equally in males and females. In light of these statistics, lupus has been called a "women's disease." To view the prevalence of lupus in men and women by ages, see Table 4.2, which summarizes some of the studies relating to sex and incidence.

The prevalence of lupus may be moderately increasing. Whether this represents a true trend or simply that our methods of ascertainment and availability of additional autoantibodies lead to diagnosing more difficult cases has not been resolved.

WHY DO PEOPLE GET LUPUS?

Lupus results when a specific predisposing set of genes is exposed to the right combination of environmental elements, infectious agents, lupus-inducing drugs, excessive ultraviolet light, physical trauma, emotional stress, or other factors. The next few chapters detail the circumstances that make certain populations more susceptible to the disorder than others.

FURTHER READING

1. Izmirly PM, Wan I, Sahl S, et al. The incidence and prevalence of systemic lupus erythematosus in New York County (Manhattan) New York: the Manhattan Lupus Surveillance Program. *Arthritis Rheumatol.* 2017;69(10):2006–2017.

2. Dall'Era M, Cisternas MG, Snipes K, Herrinton LJ, Gordon C, Helmick CG. The incidence and prevalence of systemic lupus erythematosus in San Francisco County, California: the California Lupus Surveillance Project. *Arthritis Rheumatol.* 2017;69(10):1996–2005.
3. van Vollenhoven RF. Editorial: who gets lupus? Clues to a tantalizing syndrome, *Arthritis Rheumatol.* 2017;69(3):483–486.
4. Lim SS, Drenkard C. Epidemiology of lupus: an update. *Curr Opin Rheumatol.* 2015;27(5):427–432.

Part II
INFLAMMATION AND IMMUNITY

Part I defined and classified lupus, explored the historical context of this disease, and reviewed the populations afflicted by lupus. The next two parts look at how lupus damages body tissue and why it occurs. Scientifically speaking, this is the most difficult part of the book because we tackle complex immunologic concepts and discuss how inflammation takes place. Tables and summaries are provided throughout to assist the reader. Feel free to skip this section or skim it. First, we turn to the workings of the normal immune and inflammatory response so that the abnormal responses observed in lupus will be better understood.

5
The Body's Protection Plan

Inflammatory and immune responses account for many of the symptoms observed in systemic lupus. This chapter reviews concepts of immunity and inflammation; the following chapters discuss how these concepts apply to rheumatic diseases.

WHAT ARE THE COMPONENTS OF THE NORMAL INFLAMMATORY AND IMMUNE SYSTEM?

The body is always on the lookout for foreign substances that may pose a threat to its intricate workings. Its monitoring system consists of blood and tissue components, including certain proteins and blood cells that travel back and forth between blood and tissues.

Blood Components

A 150-pound (70-kilogram) person has about 6 liters of blood, which contains several components. These include *red blood cells*, called *erythrocytes*, which are responsible for carrying and exchanging oxygen. If a person has a low count of red blood cells, she is suffering from anemia. *White blood cells*, called *leukocytes*, constitute the body's main defense system. Other blood components are *platelets*, which clot blood, and *plasma*, which includes serum. Plasma makes up most of our blood volume. It contains many proteins and other substances being carried to different parts of the body, including clotting factors that are not present in serum.

White blood cells play a central role in inflammation. Five types of white blood cells have been identified by scientists; all are relevant to lupus. These include the following.

Polymorphonuclear Cells

These cells are also called *neutrophils* or *granulocytes* and, like all other blood components, they are made in our bone marrow (blood-making parts of our bone in the pelvis and sternum). After being produced, they circulate in the blood for a few days and then pass into tissues. Some 50 to 70 percent of our circulating white cells are neutrophils.

Eosinophils

These white blood cells make up 0 to 5 percent of all our white blood cells. Their life cycle is similar to that of granulocytes. Eosinophils are involved in allergic responses.

Basophils

These cells do not have a clearly defined function and constitute less than 1 percent of our white blood cells. Tissue-based basophils are termed *mast cells*. These specialized cells combat parasitic or fungal invasion. They also play a role in allergy.

Lymphocytes

These make up 20 to 45 percent of our white blood cells and are the gatekeepers of our immune responses. Produced in the bone marrow, they migrate constantly between blood and tissue and can survive as long as 20 years. Lymphocytes can be T (thymus-derived) or B (derived from the mythical "Bursa of Fabricius") cells.

Monocytes

These cells represent about 5 percent of our circulating blood cells. They are the circulating blood component of what is called the "monocyte–macrophage" network because these cells are responsible for processing foreign materials (*antigens*) and destroying cells and tissue debris that are by-products of inflammation. In circulating blood, these cells are called monocytes; macrophages can also be present in blood, but they are mostly in tissues (see Table 5.1 and Figures 5.1 and 5.3).

Lymphoid Tissue and the Thymus

Lymphoid tissue is a key part of the immune system and represents up to 3 percent of a person's body weight. It includes our *lymph nodes* (or lymph glands), the *circulating lymphocytes*, and fixed *lymphoid tissue* (i.e., spleen). A 150-pound person has 10^{12}, or 100 billion, lymphocytes. They are widely distributed throughout the body and consist of long- and short-lived populations.

Bone marrow is the source of primitive ancestors of the *T* and *B lymphocytes*. These precursors migrate to the thymus, a gland just below the neck, which processes them into immunologically competent and knowledgeable *T cells*. These T cells provide cellular immunity and are the body's memory cells. About 70 percent of the lymphocytes are T cells. They remember what is foreign, go on to alert the body when a person re-encounters a foreign substance, and formulate a response that protects the body.

Blood is carried to tissues by the arteries and returns to the heart through the veins. Blood components, cellular waste and debris, and other materials can also

return by another system—a chain of lymph nodes that starts in our toes and fingers and ends up in the chest area. (See Figure 5.1.)

Lymphoid tissue contains T cells, *B cells*, and *natural killer cells*. B cells, which make up 10 to 15 percent of the lymphocytes, produce antibodies that eliminate what is foreign. Natural killer cells destroy targeted cells without having been sensitized to them in the past.

There are various types of T cells, which are identified by their surface markings and appearance. These types are labeled by the cumbersome term *cluster-determined*, or *CD*. Nearly all T cells have markers associated with *CD3. CD4* cells are those that "help" or promote immune responses, whereas *CD8* cells usually "suppress" or block the immune response. Approximately 50 percent of T cells have the CD4 marker, and 20 percent have the CD8 marker. Other markers are also present.

Our Antibody Response: The Gamma Globulins

When you were growing up, there may have been an occasion when your pediatrician gave you gamma globulin shots to minimize certain infections that were going around. A type of gamma globulin, *immunoglobulin*, is responsible for our antibody response. In response to an antigen our bodies produce antibodies. With appropriate signaling by T cells, B cells transform themselves into *plasma cells*. Plasma cells make immunoglobulins. These gamma globulins circulate in the plasma and protect the body from infection and other foreign material. There are five types of immunoglobulins:

IgG (immunoglobulin G) is the major antibody of plasma and the most important part of our antibody response. Most autoimmune diseases are characterized by IgG autoantibodies. IgG is made up of four subclasses known as Ig1, IgG2, IgG3, and IgG4. Deficiencies in these proteins or subclasses can lead to recurrent infections. Known as *common variable immunodeficiency, or CVID,* patients are often treated with different forms of intramuscular, subcutaneous, or intravenous gamma globulin.

IgM (immunoglobulin M) is initially produced to fight antigens but soon decreases and allows IgG to take over. It plays an important but secondary role in autoimmunity.

IgA is the major antibody of external secretions (tears, gastrointestinal tract secretions, and respiratory tract secretions). It is important in *Sjögren's syndrome* (a combination of dry eyes, dry mouth, and arthritis seen in many lupus patients) and autoimmune diseases of the bowel (ulcerative colitis and Crohn's).

IgD is poorly understood but has a role in helping B cells recognize antigens.

IgE binds to mast cells and mediates allergic reactions.

This categorization is summarized in Table 5.1 and Figure 5.1.

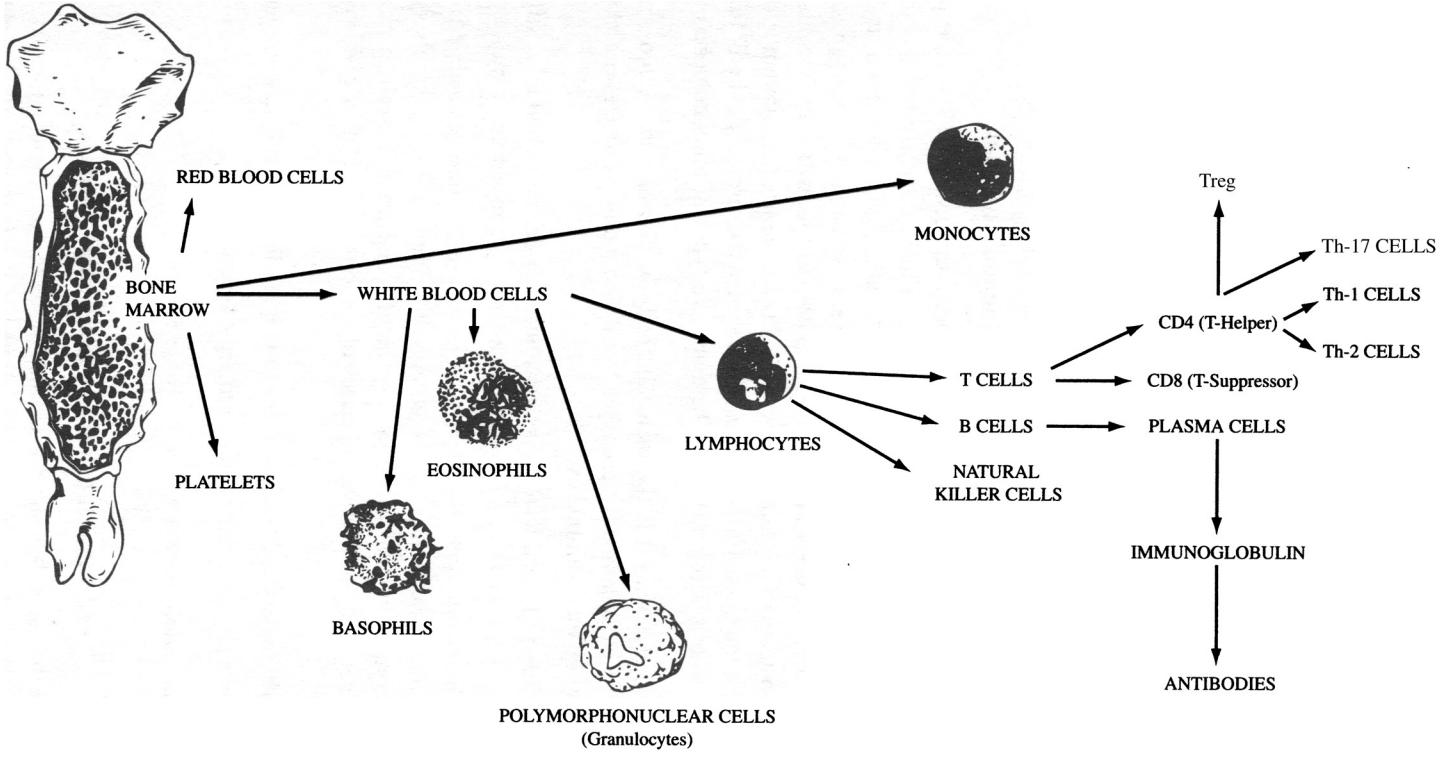

Figure 5.1. *Circulating Blood Cells*

Table 5.1. *Circulating Components of Whole Blood Important to the Immune System*

Red blood cells
Platelets
White blood cells (leukocytes)
Basophils (called mast cells in tissue)
Eosinophils
Polymorphonuclear cells (granulocytes, neutrophils)
Monocytes (called macrophages in tissues)
Lymphocytes
T cells
CD4 cells (usually helpers)
CD8 cells (usually suppressors)
Natural killer cells
B cells
Plasma (includes serum)
Albumin
Globulin
Alpha globulins
Beta globulins (includes complement)
Gamma globulins (includes immunoglobulins, listed below)
IgG (subclasses IgG1, IgG2, IgG3, IgG4)
IgA
IgM
IgD
IgE

Cytokines and Complement

Cytokines are hormonelike substances that promote various activities in the body, but in lupus their functions are altered. Cytokines play a role in the growth and development of cells and include various interleukins (mostly produced by T helper cells), chemokines (mediate chemoattraction between cells), lymphokines (make by lymphocytes), tumor necrosis factors, colony-stimulating factors (promote cell growth), and interferons. For example, interleukin-1 has many actions. Secreted during the course of an immune response, it exerts effects by binding to receptors on the cell surface. Interleukin-1 can stimulate T cells to make interleukin-2, trigger the liver to make chemicals that perpetuate inflammation, allow certain cells to proliferate, and promote the production of growth factors that, in turn, make more white blood cells and other growth factors, thus amplifying or "gearing up" the immune system. *Interferons* were originally described as proteins that interfered with the growth of viruses. Their levels are increased in the sera of lupus patients as well as in genes expressed, and they are important in the inflammatory process.

Cytokines are made by a variety of cells, especially lymphocytes and macrophages. CD4 helper cells elaborate cytokines that promote inflammation. They are called *Th-1*, or *T helper-one cells*, and go by several names: interferon, interleukin-2, and tumor necrosis factor. Other CD4 helper cells can promote the