Third Edition

A Practical Approach to Infectious Diseases

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Edited by

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Preface

This book is intended for medical students, house officers, practicing physicians, nurses, infection control practitioners, and other health care providers who treat inpatients or outpatients for infections. It should also be useful to the microbiology laboratory supervisor or technician who wants to correlate microbiology laboratory results with potential clinical implications.

The book attempts to be a practical, day-by-day guide to the diagnosis and treatment of common infectious diseases and their attendant problems; it includes specific recommendations on antimicrobial dosage, route of administration, and duration of therapy.

During the mid-1970s, we realized that there was no readily available, concise, and well-referenced book or manual discussing the approach and treatment of clinical infectious diseases and related problems. The standard textbooks contain excellent discussions of basic pathophysiology and of specific diseases of single microbial etiology, but the texts usually do not emphasize how to approach common problems such as pneumonias, sepsis of unclear etiology, wound infections, or pharyngitis. In addition, for the busy clinician who may not be able to find answers quickly in the comprehensive textbook, the outline format in this book facilitates information retrieval.

The topics discussed in the first edition of this book were selected after a careful review of the questions most often posed to the infectious disease consultation service at The Strong Memorial Hospital, Rochester, New York, over a period of several years and after assessment of the infections commonly seen in the emergency room, outpatient clinic, and office settings. New material added to the second and third editions stems in part from the questions and problems raised by medical students, house staff, attending physicians, and referring physicians at the teaching institutions represented by the contributing authors, as well as the rapidly expanding and changing developments in infectious diseases.

Based on very positive feedback about the earlier editions, we were encouraged to revise the book because of the rapid advances in antibiotic therapy and in infectious disease treatments in general. In this third edition, we have added chapters on Infections in Transplantation (Chap. 20) and Lyme Disease (Chap. 23), which supplement the chapters added in the second edition, The Immunocompromised Host (Chap. 19) (including acquired immunodeficiency syndrome—AIDS) and Antiviral Agents (Chap. 26). The Antiviral Agents chapter is a sophisticated discussion intended for the practitioner, which delineates when and why certain antiviral agents are currently useful or are anticipated to be useful.

In general, the length of the chapters has been dictated by the frequency or the importance of the clinical problems, or both. Four exceptions to this are Eye Infections (Chap. 6), Infections due to Fungi, *Actinomyces*, and *Nocardia* (Chap. 18), Infections in Transplantation (Chap. 20), and Antiviral Agents (Chap. 26). Eye and transplant infections are presented in some detail because this information is very difficult to glean from the literature and because the primary care physician may be the one who deals initially with these infections. Fungal infections are seen frequently in the compromised host and at times in the traveler, and, therefore, the

clinical aspects of these infections are discussed in some detail. Chapter 26, Antiviral Agents, provides important background information and practical clinical advice, including dosages. The last chapter, Antibiotic Use, was carefully revised in June and July of 1990 so that it is as up-to-date as possible. A carefully selected list of references follows each segment of the chapter.

There are many controversial areas in the diagnosis and management of infectious disease problems. In these cases, we try to point out several different approaches and outline our preferred approach. Each author has stressed a practical clinical approach. One of the editors (R.E.R.), who does 50 percent general internal medicine and 50 percent infectious disease consultation, has carefully tried to ensure that a useful and realistic approach is presented.

The text material was originally presented in outline format to help the reader find information as quickly as possible. We have retained this format in the second and third editions because of its popularity and usefulness. The references at the end of each chapter have been carefully selected and are often annotated to guide the reader.

We have included color photographs of a limited number of important clinical findings (e.g., rashes) that may aid in diagnosing an important infection.

In late 1987, during the early planning phases of this third edition, Dr. Robert F. Betts was invited to be the third editor along with Drs. Reese and Douglas. Dr. Betts had been involved with this book since the planning of the first edition and was a co-author of major chapters of the first and second editions.

In late 1989, Dr. Douglas decided to leave his position as Physician-in-Chief at The New York Hospital, New York, to join Merck Sharp & Dohme International. The first and second editions of this book would not have been possible without his help, support, and guidance. We are grateful for all his contributions and help.

We want to thank Marilyn Dunckel and the Word Processing Unit personnel at Office Services, The Mary Imogene Bassett Hospital, for their help in typing and preparing portions of the manuscript; and Shirley Reese for her proofreading assistance. In addition, we thank Linda Muehl (librarian), Robin L. Phillips (librarian assistant), Joseph S. Bertino, Jr., Pharm. D., Edward G. Timm, Pharm. D., Donald O. Pollock, M.D., and Alan J. Kozak, M.D., at The Mary Imogene Bassett Hospital for their useful advice; Deborah Dalton for her help with reference work; Dr. Dennis White at the New York State Health Department in Albany, N.Y., for his suggestions for the Lyme Disease chapter. We also thank Elizabeth Willingham, Sarah Boardman, Susan Pioli, and Lynne Herndon of Little, Brown and Company for their guidance throughout the publication process for this edition.

Finally, we thank our wives, Shirley and Sherrill, for their encouragement, patience, and support during the preparation of this text.

R.E.R.
R.F.B.

Contents

1

Fever and Fever of Unknown Etiology

Eugene L. Speck and
Henry W. Murray

For centuries, fever has been recognized as a characteristic sign of infection. However, fever may also be due to such noninfectious causes as tumor, collagen vascular diseases, and drugs. The pathophysiology of fever has been elucidated only relatively recently, and even in this era of sophisticated technology, the thermometer remains an essential diagnostic tool. See Murray [1] and Mandell et al. [2] for in-depth discussions of fever and fever of unknown etiology.

Fever

I. Definitions

A. Normal basal body temperature is generally accepted to be 37°C (98.6°F), determined orally. The normal figure for any given time of day varies among individuals, so the normal oral temperature range is 36–37.8°C (96.8–100°F). Rectal temperatures are higher by approximately 0.6°C (1°F).

B. Diurnal variation. Temperature is lowest in the early morning and highest in the late afternoon or early evening (4:00–8:00 PM).

1. Diurnal variation may normally be as much as 1°C (1.8°F) or more in any given individual.
2. The diurnal rhythm is consistent in each person. Its absence may suggest the possibility of factitious fever (assuming no hypothalamic disorder exists).

C. Fever and hyperthermia are physiologically two distinct processes [3]. **Fever** is said to exist whenever the body temperature rises above the peak normal range. This implies that a new temperature set point has been established, and the body actively attempts to maintain this new, higher temperature set point (see sec. **II**). Since the usual temperature range of a given individual can rarely be determined beforehand in clinical practice, any oral temperature above 37.8°C (100°F) is ordinarily considered fever.

Hyperthermia does not involve the resetting of the level of the normal temperature mechanism. Rather, heat production exceeds heat loss, as is seen in heat stroke or malignant hyperthermia.

One of the practical clinical concepts that results from this distinction is that antipyretics (drugs that lower the set point) are more effective in treating fever than hyperthermia.

D. Lethal temperature ranges

1. **The lower lethal temperature** is approximately 26°C (78.8°F) (excluding therapeutic hypothermia).
2. **The average upper lethal limit** is approximately 43°C (109.4°F). Temperatures above 41°C (105.8°F) are uncommon. On the basis of one retrospective study [4], it would appear that infections are the single most common cause (39%) of extreme temperature elevation. Thermoregulatory failure alone may account for 18%, and 32% of extremely high temperatures are caused by both thermoregulatory failure and infection occurring simultaneously [4].

   Infections likely to be associated with extreme fever are gram-negative bacteremia, Legionnaires' disease, abacteremic pyelonephritis, bacterial meningitis, viral encephalitis, typhoid fever, and malaria. Noninfectious causes of extreme pyrexia are likely to be heat stroke, intracerebral hemorrhage, hemorrhagic pancreatitis, and the malignant hyperthermia associated with general anesthesia [5, 6] or with neuroleptic drugs.

II. Pathophysiology of fever

A. Mechanisms of fever production and control [1, 7–21].

1. **The thermoregulatory center of the hypothalamus** is a small cluster of thermosensitive neurons in the hypothalamus in the region near the floor of the third ventricle. This area of the brain is believed to control body temperature and initiate fever. It appears that the region is stimulated by **endogenous pyrogens** (EPs), which probably act directly on the hypothalamus. Other mediators such as cyclic adenosine 3',5'-monophosphate (cyclic AMP), prostaglandin E_1, or serotonin may also act on the hypothalamus.
2. **Pyrogens**
   a. **Exogenous pyrogens** include viruses, bacterial products, endotoxin, bacteria, immunologic complexes, and lymphokines from sensitized lymphocytes. The pyrogenic effect of these biologic agents is mediated through the release of EPs.
   b. **EP** is a hormonelike inducible polypeptide or small protein identical to lymphocyte activating factor (LAF) and leukocyte endogenous mediator (LEM). These proteins are now referred to as interleukin-1 (IL-1). Monocytes and tissue macrophages (including Kupffer cells and splenic, alveolar, and peritoneal macrophages) are the major sources of IL-1. Vascular endothelial cells, renal mesangial cells, and cells of renal carcinomas are additional sources of IL-1. Polymorphonuclear leukocytes are not considered to be a significant source of IL-1.
   IL-1 production is stimulated by endotoxin, phagocytosis, immune complexes, tissue injury, and IL-1 itself. Glucocorticoids suppress its production. Sensitized lymphocytes, mediated through lymphokines (or cytokines), such as interferon-γ, can also stimulate phagocytic cells to produce IL-1.
   IL-1 mediates inflammation and is an immunomodulator. IL-1 activates T and B lymphocytes; this results in production of IL-2, a lymphokine capable of stimulating the proliferation of helper, suppressor, and cytolytic T cells. In vitro, increases in temperature result in enhanced stimulation of T and B cells by IL-1. IL-1 also stimulates the production of acute-phase reactants (C-reactive protein, for example), stimulates neutrophil release from the bone marrow, and sensitizes neutrophils to chemotactic signals.

B. Proposed mechanisms of fever production

1. **EP (IL-1)** binds to specialized receptors in the anterior hypothalamus and stimulates the local synthesis of prostaglandins by inducing phospholipases. Prostaglandin E appears to raise the thermal set point directly in the anterior hypothalamus.
   a. **Cyclic AMP, norepinephrine, and serotonin** act as neurotransmitters and, based on experimental evidence in animals, these transmitters may play a physiologic role in temperature control.
   b. **Prostaglandins.** IL-1 stimulates the synthesis of prostaglandins by inducing phospholipases which, in turn, make arachidonic acid available for prostaglandin synthesis.
   Aspirin and other antipyretic drugs can block prostaglandin synthesis and thereby modify temperatures. Prostaglandins can suppress the synthesis of IL-1.
2. **The hypothalamic pathways** within the hypothalamus as well as within the spinal cord and cerebral cortex (based on received information) can influence a variety of effector systems (e.g., vasomotor, respiratory, cardiac, and voluntary muscle systems). Secretion of thyroid hormones, adrenocortical hormones, epinephrine, and especially norepinephrine also may be influenced. The net result is that there are both quick (seconds to minutes) and slow (minutes to hours) responses to effect thermostasis.
   The overall effect of IL-1 on the hypothalamus is to reset the thermal set point. The response of the thermoregulatory cells of the anterior hypothalamus is to decrease heat loss and increase heat production. This is accomplished by inhibiting sweating and stimulating vasoconstriction and shivering.
   a. **Quick response.** The effector mechanisms alter peripheral blood flow,

heart rate, and respiratory rate, and they initiate shivering or sweating.

b. **Slow response** encompasses a change in the responsiveness of certain cells to norepinephrine and a change in metabolic rate under the direct influence of norepinephrine, epinephrine, thyroid hormone, corticosteroids, and probably growth hormone.

c. **Under basal conditions,** the body temperature would increase by 1°C/hour if it were not for heat loss. Heat loss is ultimately controlled by the laws of physics and involves radiation (accounting for approximately 50% of the heat loss), convection, urine, and feces. Conduction, evaporation of sweat, insensible perspiration, and warming and humidifying of inspired air collectively account for nearly 30% of heat loss.

3. **Maintenance of normal body temperature** is the result of a balance between heat production and loss. Fever results when a new set point is established: heat loss and gain are balanced at this new level.

III. **Metabolic and physiologic changes associated with fever and infection.** A variety of physiologic and metabolic alterations begin with the onset of an infection or shortly thereafter (Table 1-1) [6, 12, 22, 23]. Many of these changes are a result of the accompanying fever or the direct action of the invading microorganisms or their products.

Some metabolic changes vary during the course of an infection. For example, hyperglycemia may be a prominent feature early in the infection, whereas hypoglycemia secondary to depletion of carbohydrate stores may be troublesome later in the course of an uncontrolled infection. Serum iron and zinc tend to become less easily available to microorganisms [23].

Certain proteins, referred to collectively as acute-phase reactants, are synthesized in response to EP (IL-1) or fever. Some of these are listed in Table 1-1. Their precise roles in host defense are not entirely clear.

IV. **Fever patterns**

A. **Background.** Before the advent of modern diagnostic techniques, the pattern of the febrile response was stressed as an important diagnostic clue [6]. **Generally, a fever pattern (temperature course) cannot be considered pathognomonic for a particular infectious agent in a given patient** [24]. Nonetheless, the fever curve may be a clue to the etiology (e.g., factitious fever) of the fever.

B. **Types of patterns (temperature over time).** Since fever patterns are often discussed in the literature and at times provide some clinical clues, they are briefly summarized here.

1. **Intermittent (hectic or septic) fevers** are characterized by wide swings in temperature, with the temperature returning to normal at least once during any 24-hour period.

a. **Examples.** Irregular use of antipyretics and pyogenic abscesses are the most common causes of the intermittent pattern. It is also seen in disseminated tuberculosis, acute pyelonephritis with bacteremia, and, rarely, malaria.

b. **A double fever spike** occurring daily is said to be suggestive of gonococcal endocarditis and has been noted with miliary tuberculosis and kala-azar. It is also associated with sporadic use of antipyretics in a febrile patient.

c. **Variants of intermittent fevers**

(1) **Alternate-day fever** may be seen in *Plasmodium vivax* infections and steroid withdrawal fevers (patients on alternate-day dosage schedules).

(2) **Fever spikes** every third day occur in *Plasmodium malariae* infections.

2. **Sustained (continuous) fever** is a moderately persistent elevation in temperature with only minimal fluctuations. Examples include brucellosis, typhoid fever, tularemia, psittacosis, pneumococcal pneumonia, rickettsial infections, and in a comatose patient with central fever.

3. **Remittent fever** is similar to intermittent fever except the fluctuations in temperature are less dramatic and the temperature does not return to normal. **Examples** include acute respiratory viral infections, mycoplasmal pneumonia, and *Plasmodium falciparum* malaria.

Table 1-1. Metabolic changes associated with fever and infections

Metabolic change	Clinical significance	Comments
Metabolic rate increases approximately 12% with each 1°C elevation in body temperature	Hyperalimentation may be required, especially in chronic febrile illnesses in which the patient is unable to eat	Although anabolic processes occur, the net metabolic effect is catabolism. If the need for calories and amino acids is not met, body wasting ensues
Increased insensible water loss	Rule of thumb: There will be water increase of 300–500 ml/sq m/°C/d	Insensible loss is influenced by degree of fever, hyperpnea, humidity, and ambient temperature
Heart rate increases about 15 beats/min/°C increase in temperature	Could induce heart failure or angina in some patients	Increase in heart rate may be attenuated in the presence of typhoid fever or underlying cardiovascular disease, such as complete heart block
Hyperventilation is frequently present early in course of febrile illness	Can lead to respiratory alkalosis	Respiratory alkalosis may be seen initially in septic shock; later replaced by metabolic acidosis
Electrolyte depletion	Na^+, K^+, and Cl replacements may be necessary	Electrolyte loss through sweating, diarrhea, or vomiting
Increased levels of fibrinogen, haptoglobin, ceruloplasmin, amyloid A, synthesis of C-reactive protein, α_2-macrofetoprotein	?	May prevent utilization of trace elements by invading microorganisms; C-reactive protein combines with pneumococcal polysaccharide in vitro
Decrease availability of serum iron and zinc	?	Trace elements required for microbial growth
Activation or synthesis of humoral mediators of inflammation	To promote inflammatory response	If response "exaggerated" as in septic shock, response can be detrimental to host (disseminated intravascular coagulation)

Sources: Adapted from W. R. Beisel. Metabolic response to infection. *Annu. Rev. Med.* 26:9, 1975; C. A. Dinarello. Interleukin-1. *Rev. Infect. Dis.* 6:51, 1984; W. E. Sanders. Nonspecific Resistance to Infection, Fever, and Other Acute Phase Reactions. In L. E. Cluff and J. E. Johnson (eds.), *Clinical Concepts of Infectious Diseases* (3rd ed.). Baltimore: Williams & Wilkins, 1982. Pp. 63–74; E. D. Weinberg. Iron and infection. *Microbiol. Rev.* 42:45, 1978.

4. **Relapsing (recurrent) fever** is characterized by periods of fever and normal temperature alternating cyclically. During the febrile episodes, the fever may follow any of the previously listed patterns. **Examples** include lymphomas, rat-bite fever, borreliosis, and dengue fever.
5. **Temperature-pulse disparity** (i.e., high temperature with a relatively slow pulse) may be seen in factitious fever, brucellosis, typhoid fever, psittacosis, and Legionnaires' disease. A clue to factitious fever may be the absence of diurnal variation when there is no hypothalamic disease [6].
6. **Drug fever** may take on any of the patterns described in **1–4** above, although a sustained pattern is more common. Hectic fever spikes may simulate sepsis at times.

C. **Attenuated fever responses.** Although significant infection may exist, fever sometimes may be absent.
   1. **Seriously ill newborns** with infection may lack a fever or may even have subnormal temperatures. (In contrast, young children may have exaggerated febrile responses to relatively insignificant infections.)
   2. **Elderly patients** occasionally do not exhibit a febrile response [25] or, when febrile, have a limited response as compared to a younger patient.
   3. Patients with **uremia** may not have a fever.
   4. Patients receiving **corticosteroids** may lack a fever.
   5. **Continuous antipyretic use** may suppress fever in a patient.

V. **Why, when, and how to treat fever [26].** There seems to be a tendency—almost a reflex—among physicians to want to lower body temperature in a patient with fever. However, fever as such has not been proved harmful in humans. Temperatures in excess of 41°C (106°F) due to infection are uncommon, and temperatures in the adult in the 39–40°C (102–104°F) range do not appear to cause any brain abnormalities [17].

A. **Background.** It remains controversial whether fever affords the human any survival advantage. There is no conclusive evidence that fever serves as a mechanism of resistance to infection in humans except in neurosyphilis and gonorrheal infections that do not stimulate a temperature increase but which require a temperature in excess of 41.1°C (106°F) if they are to be treated with hyperthermia alone [3, 27–29].
   1. **Host defense mechanisms** do not seem to be adversely affected by fever.
      a. **Phagocytic activity** remains unchanged between 33°C (91.4°F) and 41°C (106°F) [29].
      b. **Antibody formation** and **complement activity** are not adversely affected by fever [27, 29, 30].
      c. **Lymphocyte transformation** is enhanced at 38.5°C (101°F) [31].
      d. **Resolution of experimental pneumococcal meningitis** is enhanced by fever [32].
      e. **Stimulation of T and B lymphocytes** by IL-1 is enhanced in vitro when the body temperature is increased from 37°C to 39°C.
      f. **Conclusion.** Controlled clinical trials for mandating control of fever in terms of host defense mechanisms are lacking. However, evidence suggesting that fever is beneficial to host defenses appears to be gradually mounting.
   2. **Some reasons not to treat fever**
      a. Since an infected patient's temperature normally decreases with appropriate therapy, the temperature curve is a helpful clue to therapeutic efficacy. Artificial suppression of the fever may create a false sense of improvement. Therefore, if the patient is tolerating the fever well, there seems little reason to suppress it.
      b. Since fever may have many causes (e.g., infections or tumors), suppressing a fever of uncertain origin may mislead the clinician and therefore should be avoided.

B. **Reasons to treat fever.** Despite the lack of evidence for the necessity of lowering temperature routinely, in certain settings such treatment is justified.
   1. **To avoid potentially harmful secondary effects** such as:
      a. **Tachycardia**, which may precipitate congestive heart failure in patients with valvular heart disease, coronary artery disease, or in elderly patients.
      b. **Febrile convulsions** in children younger than 3 or 4 years.
      c. Hypercatabolic state with **hyperventilation**, sweating and loss of fluids, exacerbating poor nutrition, underlying lung disease, or dehydration.
      d. **Encephalopathy**, particularly in the elderly.
   2. **Patient's comfort.** Although some patients are unaware of their fevers, some are very uncomfortable. Once the diagnosis is clearly established, suppression of temperature seems reasonable to make the patient more comfortable.

C. **Methods of lowering temperature**
   1. **Antipyretics**
      a. **Aspirin** is the most common and often the most effective way to reduce body temperature. However, occasionally aspirin will reduce temperatures to hypothermic levels.
         (1) **PRN administration.** If aspirin is given intermittently with fever spikes, its use may cause precipitous drops in temperature and produce a temperature chart of septic-hectic appearance. The al-