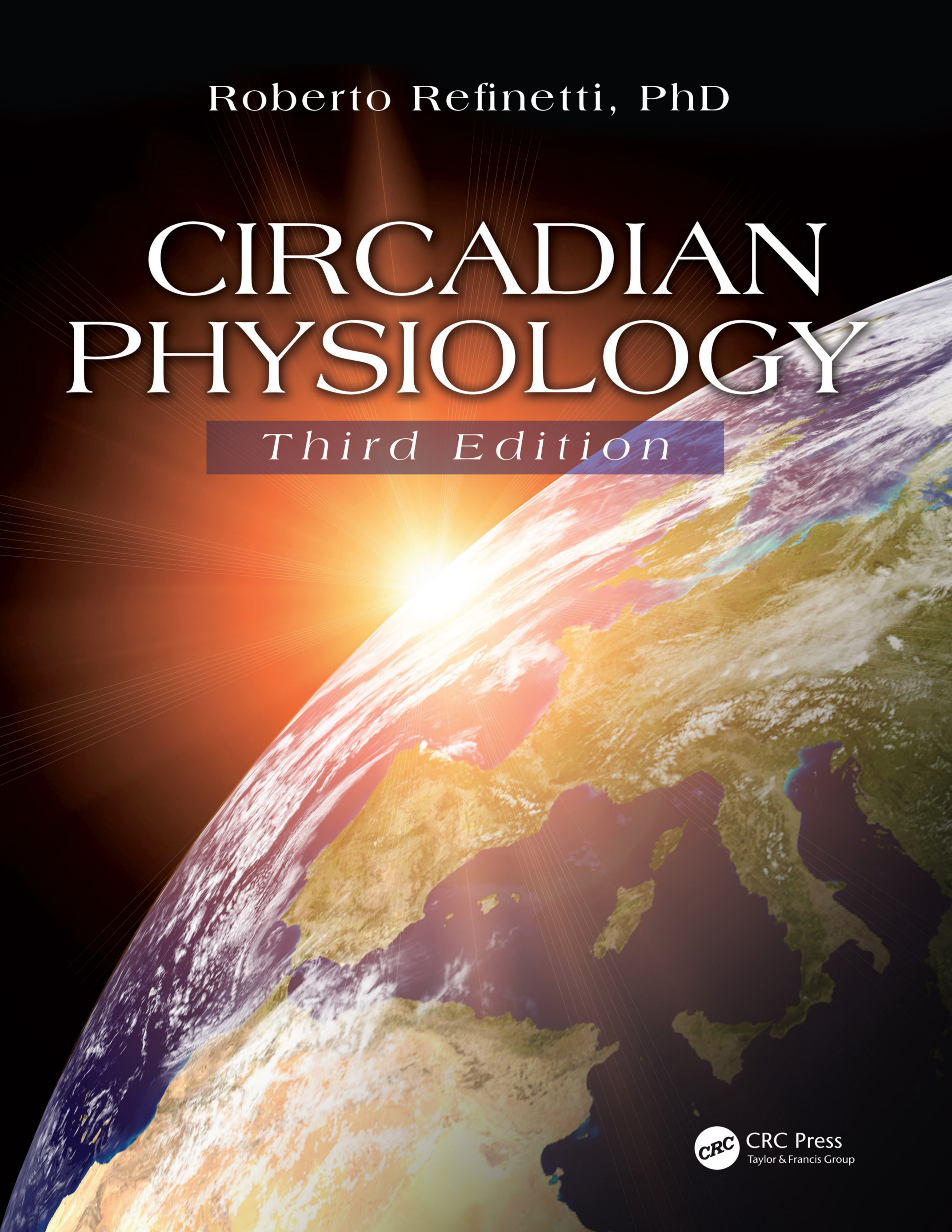

Roberto Refinetti, PhD

CIRCADIAN PHYSIOLOGY

Third Edition

CRC Press
Taylor & Francis Group

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Third Edition

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Boise State University

Idaho, USA

CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Version Date: 20160202

International Standard Book Number-13: 978-1-4665-1498-0 (eBook - PDF)

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Preface

It has been 10 years since the publication of the second edition of *Circadian Physiology*. Sales figures and comments from readers indicate that the book achieved its goal of serving as an accessible but comprehensive review of basic and applied research on circadian rhythms. A clear writing style and minimal requirement of background knowledge have allowed the book to serve both as a handbook for life scientists experienced in other fields but interested in expanding their research efforts into the study of circadian rhythms and as a textbook for undergraduate and graduate students. A Chinese translation was published in 2011. A new, updated English edition is needed now.

Readers who grew up after the universalization of the Google search engine often expect to find everything through a single online query. This is not a reasonable expectation when it comes to scientific knowledge. Scientific knowledge is very specific and requires vetting by specialists using restricted databases. Broad-minded scientists are needed to summarize the overwhelming amount of information by writing or editing a book. Several excellent books on circadian rhythms have been published in the past 10 years. Some are very readable but are targeted at general audiences that have no interest in physiological or molecular mechanisms. Others are very rigorous in content but lack comprehensive coverage of the field or adopt a writing style inaccessible to nonspecialists and students. *Circadian Physiology* remains the only book in press that successfully combines thorough and detailed coverage with an accessible writing style, providing a truly integrated view of the discipline that only a single-author book can achieve. Of course, no book can provide truly exhaustive coverage of a scientific discipline, and readers interested in more detailed information about the topics covered in this book will benefit from the detailed referencing of original sources by bibliographic footnotes in each chapter. This approach is in line with the reasoning that a good textbook is not only an effective summary of the scientific literature but also a guided gateway to this literature.

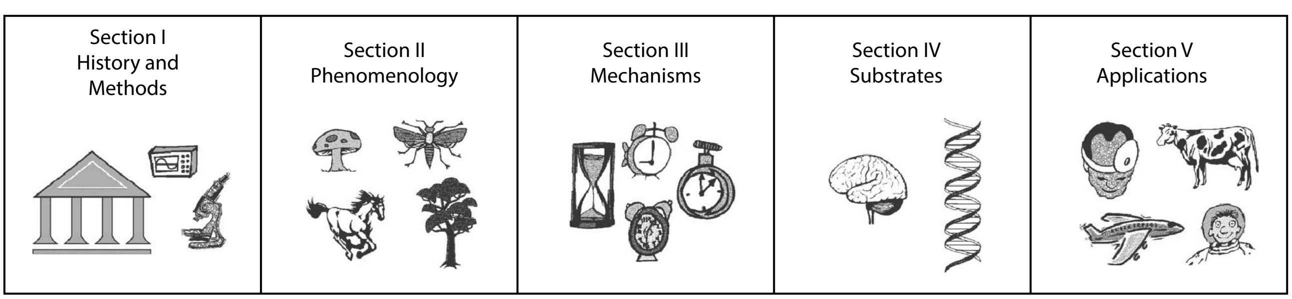
The organization of this edition is similar to that of the first and second editions because it remains the most logical and didactical. The book is divided into five sections, each with several chapters (see figure). Section I covers historical and methodological topics in the study of circadian rhythms. Section II deals with the phenomenology of biological rhythms, i.e., the description of the multiplicity of rhythmic phenomena in living organisms, including infradian, circadian, and ultradian rhythms. Section III addresses the physiological mechanisms, both endogenous and environmental, that control circadian rhythms. Section IV provides an insight into the physical substrates of circadian rhythms at the level of organs, cells, and molecules. Section V covers the multiple applications of circadian physiology in the planning of optimal times for physical and intellectual activity, the prevention of jet lag, the management of shift work, the treatment of sleep disorders, and many other endeavors.

If one thinks of biological rhythmicity as something to be learned, the five sections of the book will answer five natural questions:

Section I: How do we study it?
Section II: What is it?
Section III: How does it work?
Section IV: How is it built?
Section V: What can it be used for?

The fundamentals of circadian physiology have not changed, of course, in the 10 years since the publication of the second edition. Major advances have been made in the past decade, however, and each chapter has been updated with new material. More than a thousand references have been added, bringing the total to more than 6000 references.

This third edition of *Circadian Physiology*, like the previous ones, is intended to be accessible to a wide audience. Brief reviews of essential principles in physiology, biochemistry, molecular biology, neuroscience, statistics, computer science, and philosophy of science are provided in Chapters 2 and 3 as part of the discussion of research methods and data analysis procedures in circadian physiology. Beyond these essential principles, the required background knowledge generally does not exceed that expected of first-year university students or scientists from other fields of inquiry (and, when it does, additional background material is provided). As much as I tried to make all chapters equally readable, however, readers with different backgrounds may find some chapters to be "denser" than others. For readers who are medical or psychological practitioners, I must point out that this book was written from the perspective of circadian *physiology*, not circadian



pathology. Thus, the five sections of the book, and the chapters within them, are arranged according to basic biological processes, not according to disease types. Section V discusses important medical applications of circadian physiology, but I cannot, of course, claim to have covered circadian pathology exhaustively.

Professors adopting this edition of *Circadian Physiology* as a textbook will notice that 17 chapters are 2 chapters more than the 15 weeks of a typical university course. I felt that forcing the material into 15 chapters would disrupt the natural organization of the topics covered in the book without providing any real benefit, as many professors do not place equal emphasis on every chapter and often skip a few chapters or combine two chapters in one week. The choice of how to organize the course should rightfully remain the prerogative of the professor, not of the author of the textbook. Arrangement of the material into 17 thematically oriented chapters allows the book to present a well-organized view of the field that will be valuable not only to students but also to general readers, medical practitioners, and life scientists who are expanding their research programs into the study of circadian rhythms. Readers will notice that Chapters 8, 11, and 17 are considerably shorter than the others; they remain as separate chapters, however, for organizational reasons.

To facilitate its use as a textbook, this book contains summaries, suggestions for further readings, directions to pertinent websites, and exercises at the end of each chapter. A brief Assessment of Learning section, with 20 multiple-choice questions, appears after the last chapter. A companion CD provides computer programs designed to offer practical experience in a variety of topics. Instructions for software installation are given in a separate section before the first chapter, and programs for data analysis—and tutorials and simulation programs—are introduced at the appropriate points in the various chapters. A dictionary of circadian physiology—with information on meaning, etymology, and pronunciation—is included at the end of the book. For the benefit of international readers, the dictionary includes a table of equivalency of major circadian physiology terms in eight foreign languages. Also included are lists of standard international units of measurement and of conversion factors for various British units that are still in use in the United States. Readers—both researchers and students—are also encouraged to visit my laboratory's website (www.circadian.org) and to use the e-mail link to send me queries about specific issues.

Although it is unrealistic to expect that every reader will fall in love with this book, I hope that all readers will enjoy and benefit from reading it as much as I enjoyed and benefited from writing it. I believe that I have not only compiled a rigorous, scholarly selection of facts and theories in circadian physiology—with thorough documentation through figures and references—but have also clearly conveyed the importance and the fascination of past and current studies on the all-encompassing process of circadian rhythmicity.

Acknowledgments

Many people assisted me in the task of preparing this book. First and foremost, I thank my wife for her continued support of my academic endeavors. Early mentors—namely, Dora Ventura (University of São Paulo), Harry Carlisle and Steven Horvath (University of California, Santa Barbara), Evelyn Satinoff (University of Illinois), and Michael Menaker (University of Virginia)—were instrumental in the development of my research career. Frequent collaborations with other scientists—namely, Giuseppe Piccione and Giovanni Caola (University of Messina, Italy), Mutlu Kart Gür (Ahi Evran University, Turkey), Priyoneel Basu (Banaras Hindu University, India), Mamane Sani (University of Maradi, Niger), Lara Dugas and Amy Luke (Loyola University Chicago), and Khalid Abdoun (King Saud University, Saudi Arabia)—helped me maintain an active research program despite burgeoning administrative responsibilities. Intellectual exchanges with numerous students who worked in my laboratory over the years—particularly Aaron Osborne, Candice Brown, Adam Shoemaker, and Jonathan DeLonge—helped me avoid the stagnation of academic dogma. Several circadian researchers from around the world helped me compile the language equivalency table in the *Dictionary of Circadian Physiology*, and their names are listed in that section of the book. As the editor-in-chief of the *Journal of Circadian Rhythms*, I have also benefited greatly from the interaction with the numerous authors and members of the editorial board.

Exchanges of letters with Professor Jürgen Aschoff and Professor Franz Halberg, both pioneers in the field of circadian rhythms who are unfortunately no longer with us, helped me gain a broader historical perspective of the field.

For financial support of my research program, I thank the National Institute of Mental Health and the National Science Foundation. For comments on previous editions of *Circadian Physiology*, I thank Ralph Mistlberger (Simon Fraser University), William Timberlake (Indiana University), Colin Dawes (University of Manitoba), James Watrous (Saint Joseph's University), and Erik Maronde (Johann Wolfgang Goethe University). I also thank the various individuals and institutions that provided permission to reprint previously published diagrams and photographs, as well as individual scientists who provided original figures or their personal photographs.

Finally, this book would not have been published if it were not for the superb work of the staff at the Taylor & Francis Group. I am especially appreciative of the support and encouragement provided by Barbara Ellen Norwitz and the technical assistance provided by Jennifer Ahringer and Christine Selvan.

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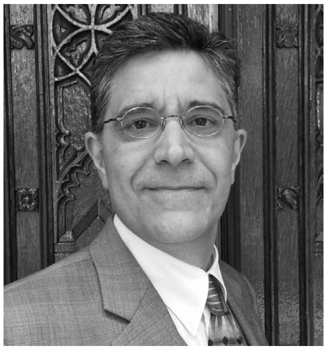
Author



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Software Installation

A CD containing the circadian physiology software package accompanies this book. Although the book can be read independently of installation and use of the software package, one's reading experience will be greatly enhanced by completion of the computer exercises that appear at the end of most chapters. Also, researchers interested in data analysis of circadian rhythms will benefit from the various data analysis programs included in the package. This section of the book explains how to install the software package and provides general information about its use.

HOW TO INSTALL THE SOFTWARE

Requirements

The programs will run under the Windows operating system. Despite recent gains in the mobile phone sector, the Mac OS continues to account for less than 7% of the desktop operating system market share, so that the development of separate versions of these programs for the Mac OS is not practical. The **Setup** program will automatically install the software package in personal computers running under Windows 10 or older versions back to Windows 95. For installation in network computers, users should consult their network administrator, who should read the **Readme** file in the distribution CD. Memory and disk space requirements are modest (no more than 40 Mb of RAM and 40 Mb of free disk space are required). A computer mouse (or equivalent) is required, but a printer is optional. Multimedia functionality (sound card and speakers) is required for only two of the programs.

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20

Procedure

Insert the *Circadian Physiology* CD in your CD drive. If the drive is set to automatically read the CD, **Setup** will start automatically. Otherwise, navigate to the CD and run the **Setup** program. Follow the simple on-screen instructions. At the end of the installation, a Shortcut will be placed on the Desktop. If you cannot find the Shortcut, see the *Troubleshooting* section.

HOW TO USE THE SOFTWARE

All programs and data files will be located in the folder "\Program Files\Circadian" unless you designated a different folder during installation of the program (sample data files will be in the subfolder "\Data"). To simplify operation of the software package, you should use the banner program **Circadian** to access the other programs. You can start **Circadian** by double-clicking on its Shortcut icon on the Desktop.

When you start **Circadian**, a banner will appear at the top of your screen. The banner contains mini icons of the various programs (see figure). To run a program, just click on its mini icon. A single click is enough. To see a brief description of the program before activating it, rest the mouse pointer on the program's icon. For your convenience, the brief descriptions are listed in the following table. The table also indicates which chapters contain exercises involving each of the programs. Detailed descriptions of the data analysis programs (i.e., programs 1 through 10) are given in the main text of Chapter 3.

No.	Name	Description	Chapters
1	Plot	Plots data as Cartesian plots or actograms	2, 3, 7
2	Moving	Calculates moving averages	3
3	Onecycle	Detects temporal pattern of a single cycle	4
4	Rhythm	Detects rhythmicity in a data set	4
5	Fourier	Conducts spectral analysis	4
6	Rayleigh	Detects periodicity in a series of events	4
7	Acro	Calculates acrophase, mean level, and amplitude of a rhythm	5
8	Tau	Calculates circadian period by chi-square periodogram	5
9	LSP	Calculates circadian period by Lomb–Scargle periodogram	5
10	Cosinor	Calculates all parameters of a rhythm	5
11	Free-run	Demonstration of free-running rhythms	12
12	Wave	Tutorial on periodic processes	3
13	Entrain	Tutorial on entrainment of circadian rhythms	7
14	PRC	Compilation of phase response curves	7, 8
15	Model	Computer model of circadian pacemaker	6 through 8

(*Continued*)

No.	Name	Description	Chapters
16	Jet-lag	How to minimize jet lag	15
17	Health	How to control your own clock	14 through 17
18	Bioclock	Listen to music (*Bioclock Rhapsody*)	17
19	Organism	Convert species names	9
20		Close the banner program	

If you have just installed the software package and are impatient to test it out, you may want to try the program **Bioclock** (number 18). This program simply plays the musical composition *Bioclock Rhapsody* and does not require any background reading. All other programs are introduced at the appropriate point in the various chapters of the book.

The menu bar in each program (except **Bioclock**) contains a Help item. Clicking on the Help item will provide you with a general description of how the program operates. More detailed instructions are given in the end-of-chapter exercises (see table). If you plan to analyze your own data sets, you must be aware that the data analysis programs (i.e., programs 1 through 10) expect data files in a specific format. For equally spaced time series, standard ASCII files (text files with one value per line) are required. For unequally spaced time series (which include time series with missing values), files must contain two values per line *separated by a space* (ASCII 32): a time tag and the value to be plotted or analyzed. The time tag must be in 24-hour clock mode (e.g., 22.5 for 10:30 p.m.). If the file contains more than 1 day, the clock may be reset to 0 at midnight each day. Sample data files are provided with the software package, and you may inspect them with a word processor to verify the file format. The sample data files are described in the Exercises at the end of the various chapters and are also listed in the following table:

File	Time Tag?	Length	Description
A01.txt	No	7 days, 6-minute resolution	Body temperature (°C) of a Richardson's ground squirrel
A02.txt	No	8 days, 6-minute resolution	Body temperature (°C) of a degu (noisy record)
A03.txt	No	36 days, 6-minute resolution	Running-wheel activity (revolutions per 6 minutes) of a golden hamster
A04.txt	No	29 days, 6-minute resolution	Running-wheel activity (revolutions per 6 minutes) of a golden hamster
A05.txt	No	42 days, 6-minute resolution	Body temperature (°C) of a laboratory rat
A06.txt	No	19 days, 6-minute resolution	Locomotor activity (beam breaks per 6 minutes) of a pill bug
A07.txt	No	6 days, 6-minute resolution	Heat production (W) of a fat-tail gerbil
A08.txt	No	20 days, 6-minute resolution	Computer-generated cosine wave, no noise
A09.txt	No	20 days, 6-minute resolution	Computer-generated cosine wave, 60% noise
A10.txt	No	20 days, 6-minute resolution	Computer-generated cosine wave, 85% noise
A11.txt	Yes	10 days	Computer-generated cosine wave, no noise
A12.txt	Yes	10 days	Computer-generated cosine wave, 60% noise
A13.txt	Yes	10 days	Computer-generated cosine wave, 85% noise
A14.txt	Yes	7 days	Body temperature (°C) of a laboratory rat
A15.txt	Yes	7 days	Body temperature (°C) of a laboratory rat
A16.txt	No	7 days, 6-minute resolution	Body temperature (°C) of a fat-tail gerbil
A17.txt	No	7 days, 6-minute resolution	Body temperature (°C) of a tree shrew
A18.txt	Yes	1 day	Locomotor activity (counts per 6 minutes) of a 13-lined ground squirrel
A19.txt	Yes	1 day	Body temperature (°C) of a man
A20.txt	No	34 days, 6-minute resolution	Running-wheel activity (revolutions per 6 minutes) of a domestic mouse with a light-induced phase shift on day 23
A21.txt	No	29 days, 6-minute resolution	Running-wheel activity (revolutions per 6 minutes) of a domestic mouse with a light-induced phase shift on day 14
A22.txt	No	43 days, 6-minute resolution	Running-wheel activity (revolutions per 6 minutes) of a Nile grass rat transferred from DD to LD on day 26
A23.txt	No	30 days, 6-minute resolution	Running-wheel activity (revolutions per 6 minutes) of a golden hamster under LD 7:5 (LD included in the file)
A24.txt	No	33 days, 6-minute resolution	Running-wheel activity (revolutions per 6 minutes) of a domestic mouse transferred from LD to DD on day 17
A25.txt	No	10 days, 6-minute resolution	Computer-generated cosine wave with periodicities of 24 and 12 hours
A26.txt	No	10 days, 6-minute resolution	Computer-generated cosine wave with periodicities of 24, 12, 10, and 6 hours
A27.txt	No	10 days, 6-minute resolution	Computer-generated cosine wave with periodicities of 24.5 and 23.5 hours
A28.txt	Yes	2 days	Air relative humidity (%)
A29.txt	No	8 days, 3-hour resolution	Plasma urea concentration (mmol per liter) of a goat
A30.txt	No	4 years, 1-day resolution	Mean daily temperature in Chicago from January 1999 to December 2002

TROUBLESHOOTING

Although all programs in the package have been extensively debugged, the possibility of minor errors cannot be ruled out. Should you have difficulties in using the software, refer to the following table that lists some of the most common problems and their solutions.

Problem	Solution
Nothing happened when I placed the installation CD in the CD drive.	The **autorun** function of your CD drive is probably disabled. You must either enable it or access the CD directly by navigating to it using the tools in the Taskbar.
The software installation failed.	Most likely, you are trying to install the software in a network computer. Call your network administrator and ask him/her to read the **Readme** file in the CD. If the installation failed in a stand-alone computer, you may consult the **Readme** file yourself. If you have a minimal knowledge of the Windows operating system, you can install the software manually. If you have limited space on your hard drive, don't copy the two *wav* files (which will save you tens of megabytes but will also prevent you from using the program **Bioclock**).
The **Circadian** shortcut icon does not appear on the Desktop.	If **Setup** failed to create a shortcut for **Circadian**, you can access the program by navigating to the appropriate folder and double-clicking on the **Circadian** icon. You may also create a Shortcut yourself. First locate the **Circadian** program. Then right-click on its icon. Choose *Create Shortcut*. Follow the simple directions. When done, drag the Shortcut to your Desktop or to the Start Menu. If you wish to rename the shortcut, right-click on it and choose *Rename*.
The banner displayed by **Circadian** is not in a convenient location on my Desktop.	Close other programs, such as word processors and web browsers. None of the programs in the circadian physiology software package will conflict with the banner.
I don't like the background color of the banner.	The background color of the banner is the same as the background color of your Desktop (which may not be visible if you have added a wallpaper to the background). Check the Display settings in the Windows Control Panel.
The tool tips (brief program descriptions) are not being shown when I rest the mouse on the program icons.	Make sure that the banner is the active window on the Desktop. To cause it to be the active window, just click anywhere between the mini icons.
When I start a program, it flashes for a few seconds.	This is only a minor nuisance, but you can avoid it by *not* double-clicking on the icons. One click is enough to start any program from the banner.
One of the data analysis programs refuses to load a data set.	Make sure that the data file is in the correct format (see specifications mentioned earlier). In particular, a data set with time tags will not load if the program is expecting a data set without time tags, and vice versa. In rare cases, it may happen that the data set is too large to be loaded all at once. If this is the case, try breaking the file down into shorter files.
I believe I am obtaining spurious numerical results.	If you live outside the United States, it is likely that you are using commas instead of periods as decimal separators. Please check the international settings in your computer (Regional and Language Options). You should use some of the data sets in the end-of-chapter exercises to make sure that you obtain the expected results before you try to analyze your own data.
A program is not doing what it is supposed to do.	It is possible that *you* are doing something wrong. Check the Help item in the program's menu bar.
A program supposed to have audio functionality remains silent.	"You have the right to remain silent" should apply to people being arrested, not to computer programs! First of all, check the volume in your speakers. If this is not the problem, make sure that your computer has the necessary hardware (sound card, speakers, etc.).
Data analysis procedures take too long to execute.	No procedure should take more than a few seconds. If you have a large data set, you may be able to speed up processing by closing other programs that are simultaneously open. If your computer runs at less than 1 GHz, you may want to upgrade it.
When I print something, the page comes out blank.	Check your printer settings. All programs in this software package utilize the Windows printing routines for the default printer. If the Windows printer settings are not correct, the information will be lost on its way to the printer.
Some text appears in fonts that are too big or too small for the program window.	The programs use standard fonts in computers sold in the United States. In other countries, it is possible that the closest font set available in the computer will not be adequate. You should obtain and install font sets for MS Sans Serif (8 point and 10 point sizes) and Courier New (8 point size). Check Microsoft's website (www.microsoft.com).
In some programs, some words have spurious characters.	Encoding of characters does not have a universal standard. The programs in this package use Western European Windows encoding. If your computer is set for a different encoding, some characters will not print correctly. Check the Fonts settings in the Windows Control Panel.
The program window is too big and extends outside the borders of the screen.	Your video settings are archaic. Use the Windows Control Panel to set the resolution of your monitor to 1024×768 pixels or greater. Color settings should not be a problem (a 16-bit color scheme is sufficient).
I tried everything in this Troubleshooting list and am still having problems.	Ask for help from the author of the program. Send an e-mail message to Dr. Refinetti at refinetti@circadian.org. Please include information about your computer and a detailed description of the problem.

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Section I

History and Methods

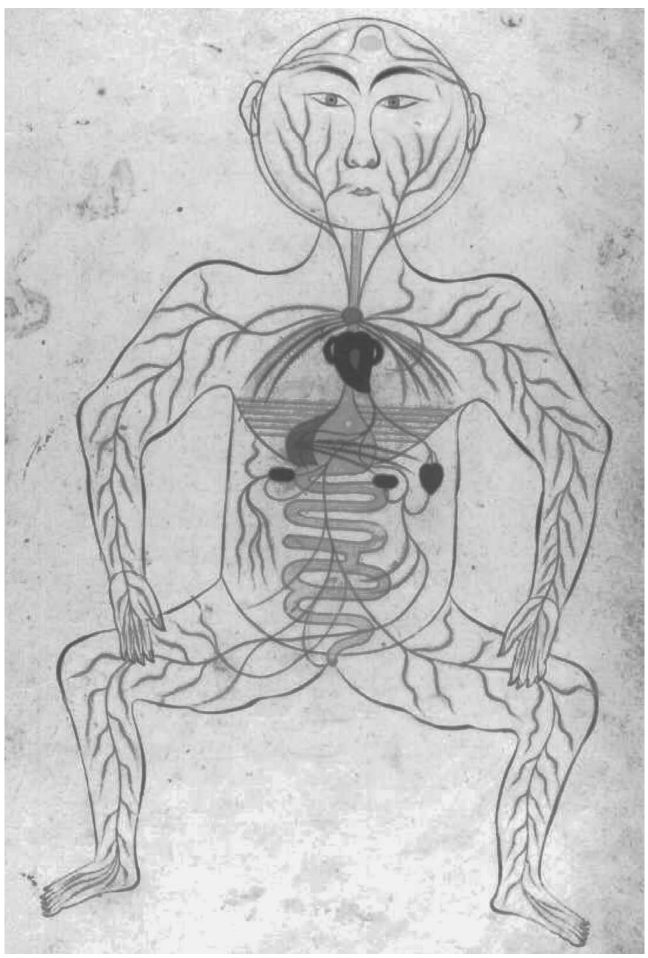

Illustration of human anatomy drawn by Persian physician Mansur ibn Mohammed in 1396. (Image courtesy of the Clendening Library at the University of Kansas Medical Center, Kansas City, MO.)

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1 Early Research on Circadian Rhythms

1.1 REMOTE PAST

This chapter deals with the history of circadian physiology—from ancient times to the present. Before we address its history, we must define circadian physiology. *Physiology* (or "integrative biology") is the study of vital processes of living organisms, particularly at the level of organs and organ systems and at the level of the organism as a whole.[1] Because physiological processes are dependent on anatomical and biochemical factors, and because they constitute the physical basis of behavior, the discipline of physiology must incorporate the disciplines of anatomy, endocrinology, molecular biology, pharmacology, neuroscience, and psychology. *Circadian physiology* is the branch of physiology that deals with the temporal organization of vital processes in the course of a day. Thus, circadian physiology is integrative biology at its best: it deals with the integration of functions in both the spatial and temporal dimensions. A discussion of the conceptual and practical importance of circadian physiology will be initiated in Section 1.3 and will continue throughout this book.

Written records of observations in circadian physiology are by necessity limited to the few millennia since the invention of written language. However, it is very likely that early humans were aware of daily variations in physiological processes. At the very least, they must have been aware of daily rhythmicity in the environment and its impact on their own daily cycle of wake and sleep. Awareness of daily rhythmicity in the environment is evidenced by the creation of various forms of clocks and calendars. The sundial, which indicates the time of day as a function of the size and direction of the shade cast by the sun (Figure 1.1), was perhaps the first man-made clock. The Egyptians erected obelisks that were used as sundials more than 5500 years ago.[2] The Chaldeans, in Mesopotamia, created a sophisticated system of time measurement about 3000 years ago,[3] a system from which our own time measurement system is derived. In the Chaldean system, a day was divided into 12 long hours instead of into the shorter 24 hours that we adopt today, but their system was at the origin of our nondecimal division of the day. A decree issued in France in 1793 established a decimal division of the day, but it was revoked 2 years later.[4] Except for this brief diversion, the partition of a day into 24 hours, and of an hour into 60 minutes, has been a global standard for centuries. Usage of the system differs in different regions of the world up to this day, however. In the United States, only scientists and the military use a true 24-hour system; businesses and ordinary citizens use a double 12-hour system with 12 hours before noon (*ante meridiem*) and 12 hours after noon (*post meridiem*), as indicated in Figure 1.2. In many other parts of the world, official times are given in the 24-hour system (such as *20:30 hours* for a dinner invitation) but a 12-hour system is used in informal conversation (such as *8:30 at night* for an informal get-together with friends). The colon between hours and minutes is often replaced by a period in many countries (e.g., 9:14 a.m. = 9.14 hours) and is usually omitted in the American military notation (e.g., 5:35 p.m. = 1735 hours).

For longer time intervals, most contemporary human societies use the Gregorian calendar, which combines days into weeks (with 7 days in a week), weeks into months (with approximately 4 weeks in a month), months into years (with 12 months in a year), years into decades (with 10 years in a decade), decades into centuries (with 10 decades in a century), and centuries into millennia (with 10 centuries in a millennium).[5] Dates are usually expressed in terms of day, month, and year, with "year number one" being the year in which past historians believed that Jesus Christ had been born. Thus, for instance, the date of the beginning of World War II was the first day of September in 1939.[3] In the United States, the month usually precedes the day in the writing of dates, which can be very confusing if day and month are expressed numerically. Thus, for example, "9/11" in the United States refers to the 11th day of September, not the 9th day of November as it does in most of the rest of the world. To avoid confusion, some scientists express dates in the form of year-month-day (such as "2001/9/11" or "2001-9-11") to make it clear that the elements are inverted. To reference years before year 1, a regressive calendar is used with a special notation. Thus, for example, Roman leader Julius Caesar was born in the year 100 BC (100 Before Christ) or 100 BCE (100 Before the Common Era).[3] To avoid ambiguity, years after year 1 are sometimes, although not often, also expressed with a special notation. For instance, this book was published in the year AD 2016 (Anno Domini 2016) or 2016 CE (2016 of the Common Era).

1.1.1 Biological Rhythms

Jürgen Aschoff, a prominent twentieth-century circadian physiologist whose contributions will be discussed later in this chapter, believed to have identified *Archilochus* as the author of the oldest written record of observations in circadian physiology.[6] Archilochus (675–635 BC) was a Greek poet whose verses remain only as fragments today.[7] The fragment to which Aschoff alluded is shown in Figure 1.3. The critical passage is the last sentence, which can be translated as: "Recognize what sort of rhythm governs man." The historical problem here is how to determine what Archilochus meant by the term *rhythm* (ρυσμος). The fragment advises the reader to stand and fight in life, not to openly rejoice after

FIGURE 1.1 A nineteenth-century sundial in Budapest, Hungary. Sundials are one of oldest instruments devised by humankind to measure the passage of time. (Photo courtesy of Miroslav Broz, Hradec Králové, Czech Republic.)

a victory or to cry after defeat, to enjoy the good times and not to regret the bad times. In this context, it would seem that *rhythm* means merely a lack of constancy, not a true recurring or oscillatory process—that is, not really a rhythm. As a matter of fact, the same verse has been translated with the word *motion* instead of *rhythm*: "A measured motion governs man."[8] Thus, it is inaccurate to identify Archilocus as the author of the oldest written record of observations in circadian physiology.

It is only three centuries later, in the fourth century BC, that we find an unambiguous written record of observations in circadian physiology. This was when *Androsthenes of Thasus*, a ship captain under the command of Alexander, the Great, (Figure 1.4), recorded his observations of daily movements in plants.[9] Androsthenes traveled through North Africa and India and had the chance to observe the daily movement of the leaves of the tamarind tree (*Tamarindus indica*).

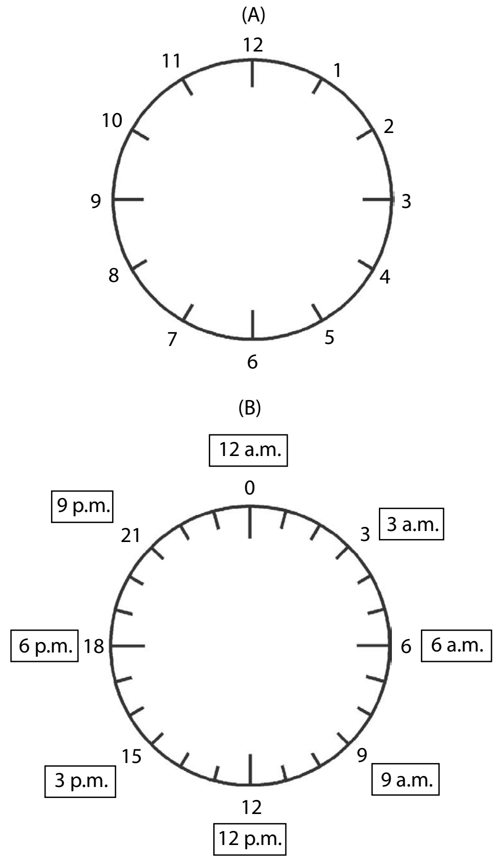

FIGURE 1.2 Diagrams of (A) a 12-hour clock and (B) a 24-hour clock. Although analog clocks almost always have 12-hour dials, a full day has twice as many hours. In most of the world, time of day is expressed according to a 24-hour clock. In the United Sates, a day is divided into 12 hours before noon (*ante meridiem*, or a.m.) and 12 hours after noon (*post meridiem*, or p.m.).

Although most of us think of plants as dull, motionless organisms, Androsthenes noticed that the tamarind leaves exhibit an impressive daily cycle of movement, wherein the leaves move up during the day and down at night. Even if not as impressive, a similar daily movement of leaves can also be seen in the common bean plant (Figure 1.5). For those interested, Exercise 1.2 (at the end of this chapter) provides instructions on how to monitor the leaf movement of the bean plant.

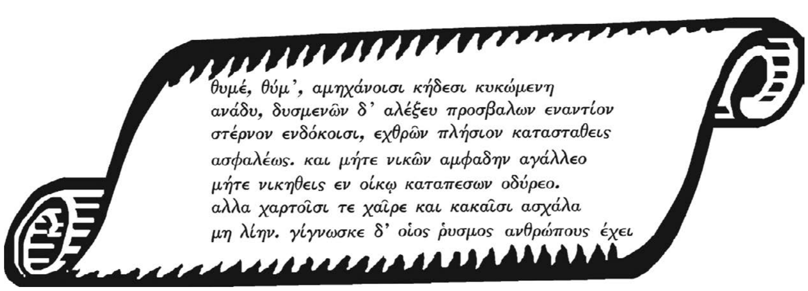

FIGURE 1.3 Is it "Greek" to you? It is Greek. This is a fragment of a poem written around 650 BC by the Greek poet Archilochus. It talks about the rhythms of life.

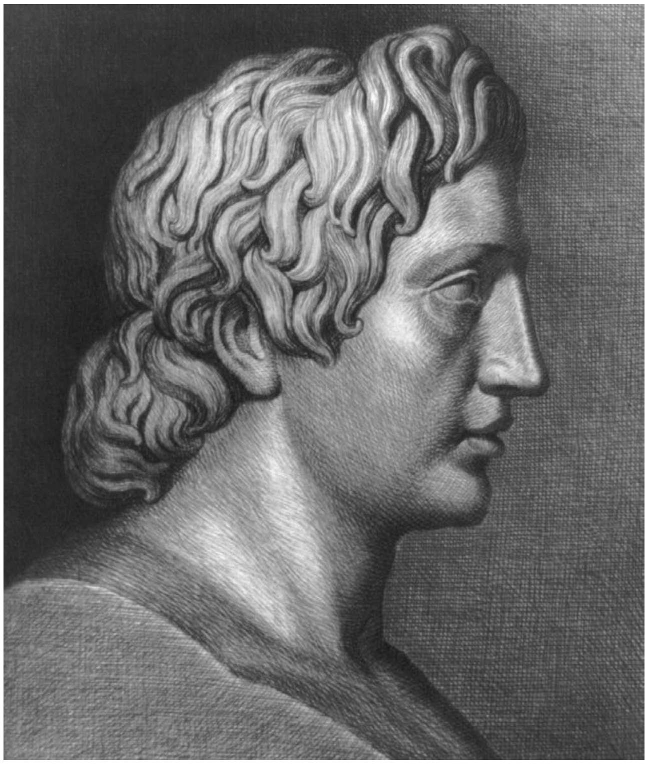

FIGURE 1.4 Alexander the Great (356–323 BC). The great Greek (Macedonian) general conquered most of the civilized world in the fourth century BC. One of the many ship captains in his fleet was Androsthenes of Thasus, who wrote the first description of daily movements in plants. (Courtesy of Library of Congress, Washington, DC.)

Other noteworthy observations of daily rhythmicity during antiquity were those of the great physicians *Hippocrates* and *Galen*.[6,10] Hippocrates (460–370 BC), the Greek healer heralded as the father of medicine, made several observations about periodic physiological processes, such as the recurrence of fever in 24-hour intervals. Galen (130–200 AC), physician to Roman emperors Marcus Aurelius and Commodus, recorded detailed descriptions of *paroxysms* (outbursts of symptoms with recurring manifestations, such as the chills of malaria). Neither Hippocrates nor Galen—nor, as far as we know, anyone in antiquity—considered that daily physiological rhythms might be caused not only by environmental factors (such as the alternation of day and night) but also by an endogenous clock (i.e., by a process that takes place inside the organism and persists in the absence of daily environmental cycles).

1.1.2 Endogenous Rhythmicity

Many commentators on the history of circadian physiology point to *Jean-Jacques de Mairan* (Figure 1.6) as the first person to demonstrate that daily rhythms may be endogenously generated.[11–13] Mairan (1678–1771) was a French astronomer and part-time botanist. He observed the *sensitive* plant (*Mimosa pudica*), which owes its name to the fact that its leaves fold up when touched. Unlike the vertical movement of the leaves of the tamarind tree, the leaves of the sensitive plant fold up along the midline at night and open up during the day. Mairan placed a sensitive plant in a totally dark place and noticed that the leaves still opened up in the morning and folded up in the evening.[14] This indicated that the daily rhythm of leaf folding does not require a daily

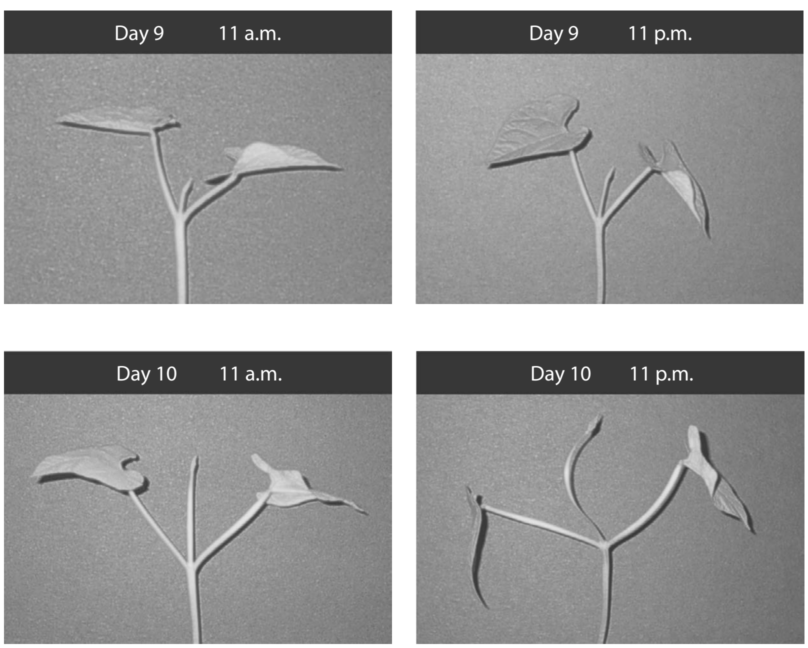

FIGURE 1.5 The "sleep" cycle of the bean plant. The leaves of the common bean plant (*Phaseolus vulgaris*) rise during the day and drop at night. (Photo and montage by R. Refinetti.)

FIGURE 1.6 Jean-Jacques Dortous de Mairan (1678–1771). This French astronomer and botanist was the first to describe the daily movement of the leaves of a plant kept in isolation from the daily cycle of light and darkness. (Courtesy of Wolfgang Steinicke, Umkirch, Germany.)

rhythm of sunlight. However, this observation alone does *not* demonstrate the existence of endogenous rhythmicity. Other environmental factors besides light might have caused the leaves to open up. As a matter of fact, Mairan's report to the French Royal Academy of Sciences concluded that "the sensitive plant perceives the sun without seeing it,"[14] thus conceding that, in his opinion, the persistent rhythmicity had an exogenous cause.

A younger contemporary of Mairan, *Henri Louis Duhamel du Monceau* (Figure 1.7), also contributed to the history of circadian physiology. A compatriot of Mairan, Monceau (1700–1782) was a botanist and naval engineer. He replicated and expanded Mairan's observations by keeping a sensitive plant inside a vault, where neither light nor temperature oscillated.[15] Like Mairan, Monceau noticed that the leaves of the plant still opened up in the morning and folded up in the evening, but he did not postulate an endogenous source of the rhythmicity.

Much more of a circadian physiologist, although also lacking an explicit notion of endogenous rhythmicity, was *Christoph Wilhelm Hufeland* (Figure 1.8). A German physician, Hufeland (1762–1836), was the creator of the discipline of *macrobiotics*, the study of the prolongation of life.[16] In his acclaimed 1797 book, *The Art of Prolonging Life*, he expressed many concepts of physiological rhythmicity and pointed out that the 24-hour period of the Earth's revolution is reflected in organic life and appears in all human diseases.[17]

FIGURE 1.7 Henri Louis Duhamel du Monceau (1700–1782). This French botanist and naval engineer repeated and expanded Mairan's observations on the daily movement of leaves. (Courtesy of Wikimedia commons.)

FIGURE 1.8 Christoph Wilhelm Hufeland (1762–1836). This German physician wrote the first systematic account of daily rhythmicity in human physiology as part of a larger book. (Courtesy of Clendening Library, University of Kansas Medical Center, Kansas City, MO.)

FIGURE 1.9 Julien Joseph Virey (1775–1846). The doctoral dissertation of this French pharmacist was the first book devoted to biological rhythms. (Courtesy of Library of the National Academy of Medicine, Paris, France.)

FIGURE 1.10 Augustin Pyramus de Candolle (1778–1841). This Swiss botanist was the first to document a circadian rhythm with a period different from 24 hours (and, therefore, not attributable to geophysical factors). (Courtesy of Library of the Russian Academy of Sciences, Moscow, Russia.)

His contemporary, *Julien Joseph Virey* (Figure 1.9), went a step further and wrote the first book (actually his doctoral dissertation in medical school) dedicated to daily rhythmicity in physiological processes.[18] A French pharmacist, Virey (1775–1846), did not defend his medical dissertation until he was 40 years old, but only a few years later, he was invited to write the entry on Periodicity for the encyclopedic *Dictionary of Medical Sciences*.[10] He believed that circadian rhythms were endogenously generated, but his actual research was restricted to the careful description of daily rhythms in diseases and mortality.[19]

The honor of first describing research that demonstrated the endogenous nature of circadian rhythms seems to belong to *Augustin de Candolle* (Figure 1.10). A renowned Swiss botanist, Candolle (1778–1841) studied the rhythm of folding and opening of the leaves of the sensitive plant, as Mairan had done a century earlier. Candolle observed that the rhythm persisted under continuous illumination, similarly to what Mairan had observed. Importantly, however, Candolle noticed that the period of the rhythm (i.e., the duration of the cycle) was shorter than 24 hours.[20] This finding was important because the period of the rhythm should have been exactly 24 hours if some uncontrolled geophysical factor had been responsible for the rhythm. A period shorter than 24 hours meant that a different clock had to be responsible for the rhythm—and, if the clock was not outside the plant, it had to be inside. Thus, Candolle effectively demonstrated the existence of an endogenous circadian clock.[21] Where exactly this endogenous clock is located and how it operates remained unknown for another 100 years.

Many other researchers investigated biological rhythms during the nineteenth century. Unfortunately, some were less trustworthy than others. One theory that deserves mention because of its surprising popularity (despite its absurdity) is that of *biorhythm*. The notion of biorhythms was developed late in the nineteenth century by two individuals working independently: German physician Wilhelm Fliess (1859–1928) and Austrian psychologist Hermann Swoboda (1873–1963). According to followers of Fliess and Swoboda, biorhythms are three natural cycles within the human body that affect us physically, emotionally, and intellectually.[22–25] The three biorhythms begin when a person is born, and they oscillate with absolute precision, as perfect sine waves, until the person dies. The *physical* rhythm regulates physical strength, energy, endurance, sex drive, confidence, and so forth. The *emotional* rhythm governs creativity, sensitivity, mood, and so on. The *intellectual* rhythm is associated with intelligence, memory, mental alertness, logical thinking, and so on. The physical rhythm is 23 days long; the emotional, 28 days long; and the intellectual, 33 days long (Figure 1.11). The different lengths of the three cycles cause them to be constantly out of phase (they coincide only at birth and every 58 years plus 66 or 67 days thereafter, depending on the number of leap years in between). Thus, a person's disposition on any given day will be a composite of the states of the three rhythms. By calculating and studying one's biorhythms, one is supposedly capable of knowing what to expect each day and, therefore, one is capable of avoiding bad experiences. Yet, neither Fliess and Swoboda nor their followers ever bothered to

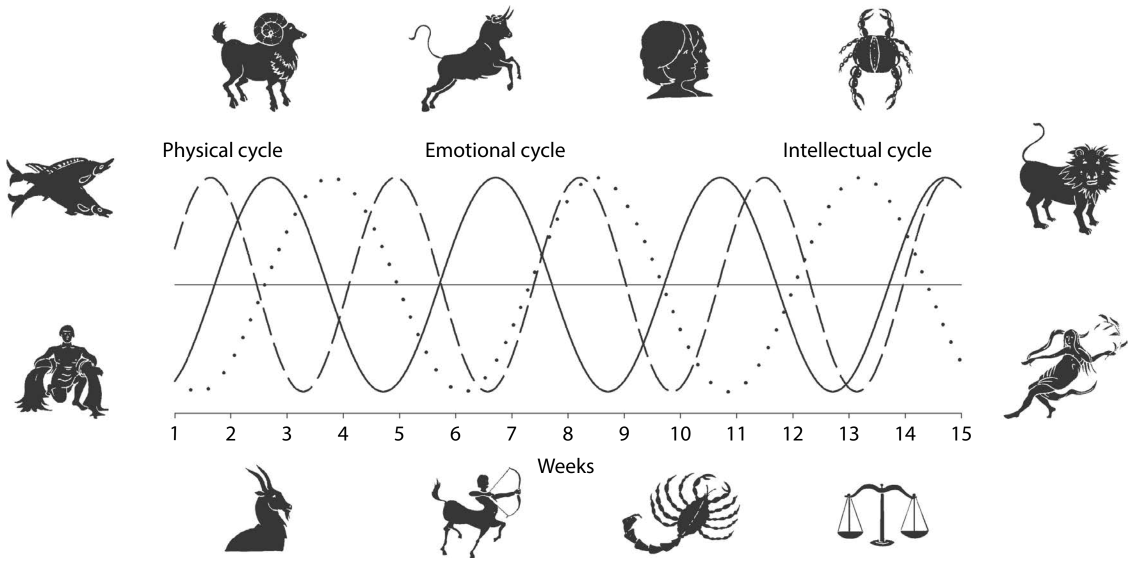

FIGURE 1.11 Biorhythms and horoscope? The concept of biorhythms was developed by W. Fliess and H. Swoboda in the late 1800s. Although they claimed no connection with the signs of the zodiac, their notion of biorhythms was just as unscientific as horoscopes are. (Data from Crawley, J., *The Biorhythm Book*, Journey, Boston, MA, 1996; Signs of the zodiac after Fisher, D. and Bragonier, R., *What's What*, Hammond, Maplewood, NJ, 1981.)

conduct actual research to verify the veracity of the theory. As a matter of fact, the essence of the theory reveals its concocted nature. As we will see throughout this book, real biological rhythms have a pattern that allows us to identify them as actual rhythms, but they are clearly subject to biological variability. Even something as mundane as one's bedtime expresses regularity with variability. You probably go to bed at about the same time each night (say, 11 o'clock or midnight), but rarely do you keep your bedtime with the accuracy of minutes (and certainly not of seconds). Variability is an essential feature of biological processes,[26] to such an extent that absence of regular variability is often a sign of disease[27] and is associated with mortality risk in middle-aged and elderly people.[28] In contrast, biorhythms are amazingly "clean" rhythms that allegedly repeat themselves for the whole life of the individual without ever deviating, even slightly, from a perfect sine wave. This extreme proposed regularity demonstrates that the theory was developed in someone's head without any observation of actual biological processes. Not surprisingly, a careful review of research on biorhythms yielded the conclusion that "biorhythm theory is not valid."[29]

In contrast to the "armchair" work of Fliess and Swoboda, physician John Davy actually recorded his own body temperature (under the tongue) in the morning and evening every day for nine consecutive months in 1844.[30] Figure 1.12 shows a 1-month segment of his data. Notice that the temperature goes up and down reliably each day but that there is also considerable variability from one day to the next. With only two measurements per day, Davy could not have a close look at the daily oscillation of his temperature. However, 22 years later, physician William Ogle recorded his own temperature several times a day for several months.[31] As can be seen in Figure 1.13, the averaged readings display clear daily rhythmicity with a peak in the evening and a trough in the early morning. Notice that even the averaged values do not form a smooth sine wave; rather, they show irregularities typical of true living beings. Many other individuals conducted empirical research on the daily rhythmicity of bodily functions in humans[32–34] and other animals[35–38] through the end of the nineteenth century.

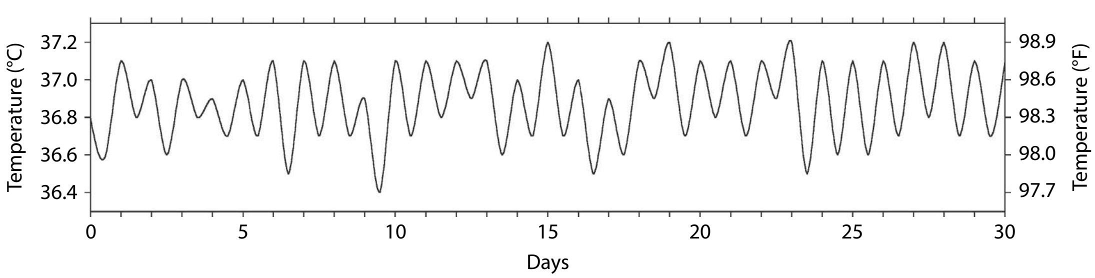

FIGURE 1.12 A real biological rhythm. In 1844, British physician John Davy made accurate measurements of the day-to-day variation of his own body temperature. (Data from Davy, J., *Philos. Trans. R. Soc. Lond.*, 135, 319, 1845.)

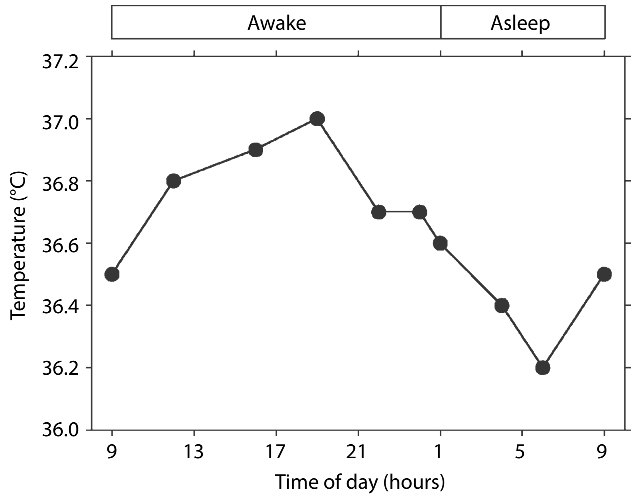

FIGURE 1.13 An early record of the daily rhythm of body temperature. In 1865, physician William Ogle conducted measurements of his own oral temperature with temporal resolution high enough to allow the characterization of a daily rhythm. (Data from Ogle, W., *St. George's Hosp. Rep*., 1, 221, 1866.)

1.2 TWENTIETH CENTURY

The twentieth century witnessed a surge in sophisticated research on circadian rhythms. Historical research is made difficult by the fact that major biomedical databases, such as the U.S. National Library of Medicine's PubMed database, have records going back only to the 1950s, but manual inspection of old library collections allows one to identify quite a few pre-1950 studies. Many of these studies, and many others published during the second half of the twentieth century, made fundamental contributions to the current knowledge in circadian physiology.

1.2.1 1901–1950

From 1902 to 1905, Sutherland Simpson and J. J. Galbraith, in Scotland, conducted detailed studies of the body temperature rhythm of monkeys maintained under light-dark cycles, constant light, and constant darkness.[39] An example of their experimental results in rhesus monkeys is shown in Figure 1.14. Body temperature clearly rises during the light phase of the daily cycle, peaks at the beginning of the dark phase, falls through the night, and then follows a similar but not identical pattern on the second day. Also at the beginning of the twentieth century, Francis Benedict, in Connecticut, and Arthur Gates, in California, conducted detailed measurements of the body temperature rhythm[40] and of daily variations in memory[41] in human subjects. None of these investigators, however, was concerned with the origin of the rhythms (i.e., whether the rhythms were caused by environmental cycles or were endogenously generated).

The first demonstration of the endogenous nature of circadian rhythms in an animal species was provided by Maynard Johnson, in Illinois, in 1926.[42] Johnson studied the rhythm of

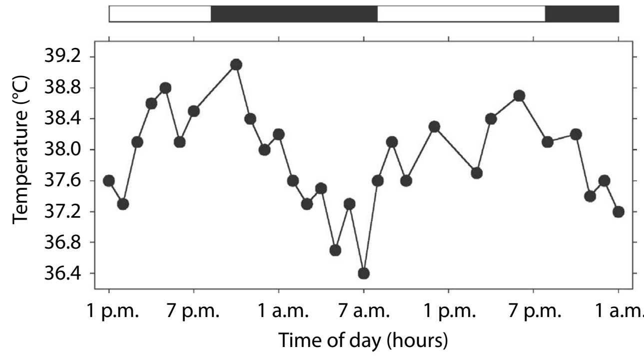

FIGURE 1.14 Old records of body temperature of a monkey. From 1902 to 1905, Simpson and Galbraith conducted numerous measurements of the body temperature of rhesus monkeys, as exemplified in these records from Monkey #31. The light and dark bars at the top of the figure indicate the approximate duration of the light and dark phases of the prevailing light–dark cycle. (Data from Simpson, S. and Galbraith, J.J., *Trans. R. Soc. Edinburgh*, 45, 65, 1906.)

locomotor activity (i.e., the rhythm of moving around) of deer mice (*Peromyscus leucopus*). He kept the mice in constant darkness in an environment without temporal cues and examined the time at which the animals became active each day (the "onset time"). As shown in Figure 1.15, the activity onsets drifted 4 hours (from 4 p.m. to 8 p.m.) in about a month—again, with some day-to-day variability. Thus, the activity onsets were delayed by about 6 minutes each day. This means that the mice were running on a 24.1-hour clock rather than on a 24.0-hour clock. Because all potential geophysical time cues would be expected to run on a 24.0-hour clock (the period of Earth's rotation), Johnson justifiably concluded that the clock responsible for the activity rhythm of the mice was

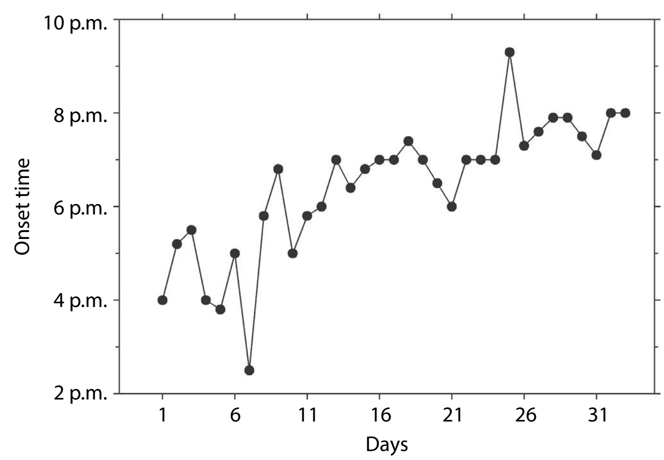

FIGURE 1.15 "Free-running" mouse. In 1925, Maynard Johnson documented a circadian rhythm of locomotor activity in deer mice (*Peromyscus leucopus*) maintained in constant darkness. The rhythm exhibited a period longer than 24 hours and, therefore, could not be attributed to geophysical factors. "Onset time" refers to the time each day when the mouse initiated activity. (Data from Johnson, M.S., *J. Mammal*., 7, 245, 1926.)

endogenous, not exogenous. This issue will be discussed in greater detail in Chapter 6.

Just 4 years later, L.A. Rogers and G.R. Greenbank reported the existence of a daily rhythm of growth in colonies of bacteria (*Escherichia coli*).[43] Representative records are shown in Figure 1.16. Despite a considerable amount of noise, clear daily rhythmicity can be seen. Rogers and Greenbank did not investigate whether the growth rhythm was endogenously generated, but their study was important because it showed daily rhythmicity in a *prokaryotic* organism (i.e., a unicellular organism without a membrane separating the nucleus from the cytoplasm), thus implying that daily rhythmicity is not restricted to more complex *eukaryotic* organisms and, therefore, is probably a characteristic of all life on Earth. We will return to this topic in Chapter 9.

Before the end of the decade of 1930, enough knowledge on daily rhythms was available to justify a literature review of the topic by John Welsh[44] and to stimulate discussion of potential medical uses of this knowledge by Arthur Jores.[45] A very influential researcher at this time was the German botanist *Erwin Bünning* (Figure 1.17). Bünning (1906–1990) worked at the universities of Jena, Königsberg, and Tübingen. His central interest was in photoperiodism (the physiological response of organisms to seasonal changes in light), but his research on the role of light in plant physiology provided several insights into circadian physiology. As we will see in Chapter 7, Bünning proposed, as early as 1936, an explanation of photoperiodism that involved a mechanism now believed to be essential for the synchronization of circadian rhythms to the environmental light–dark cycle.[46] Bünning's contribution to circadian physiology also included the writing of the first comprehensive book in the field, *The Physiological Clock*. The book was originally published in German in 1958[47] and later in three English editions, the last one of which appeared in 1973.[48]

Two other researchers who contributed significantly to the progress of circadian physiology in the early twentieth

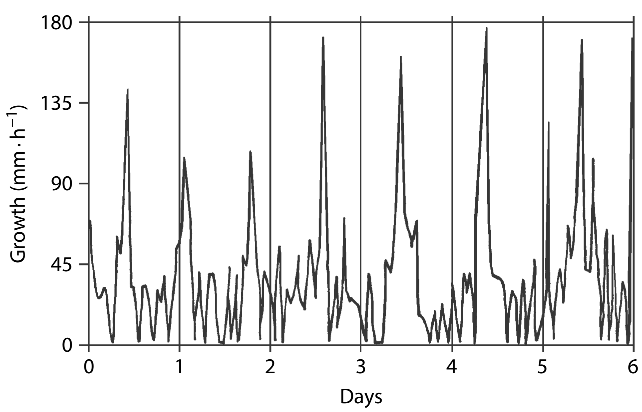

FIGURE 1.16 Daily rhythmicity in prokaryotes. In 1929, Rogers and Greenbank demonstrated the existence of daily rhythmicity in the growth of bacteria, which are prokaryotes (i.e., organisms whose cells do not have a separate nucleus). Except in the second of the 6 days shown, clear daily peaks of growth can be seen. (Data from Rogers, L.A. and Greenbank, G.R., *J. Bacteriol*., 19, 181, 1930.)

FIGURE 1.17 Erwin Bünning (1906–1990). This German botanist, whose central research interest was in the mechanism of photoperiodism, made significant contributions to the study of circadian rhythms in the twentieth century. (Courtesy of Botanical Archive, University of Hamburg, Hamburg, Germany.)

century were Curt Richter (1894–1988), a psychology professor at Johns Hopkins University who conducted extensive research on circadian rhythms in laboratory animals and human patients,[49] and Nathaniel Kleitman (1895–1999), the renowned investigator of the physiology of sleep at the University of Chicago who studied circadian rhythms in humans.[50]

1.2.2 1951–2000

Starting in the 1950s, many investigators concentrated their full-time efforts on research in circadian physiology, and three individuals in particular became so influential as to justify the honor of being called the *forefathers* of modern circadian physiology. They were Jürgen Aschoff, Franz Halberg, and Colin Pittendrigh.

Jürgen Aschoff (Figure 1.18) was born in Freiburg, Germany, in 1913 and spent most of his professional life at the Max Planck Institute for Behavioral Physiology, in Andechs. Originally a thermal physiologist, he gradually switched to the study of circadian rhythms.[51] He was interested in all manifestations of circadian rhythmicity, in the laboratory as well as in the field. An avid researcher, he investigated a wide variety of phenomena in a multitude of species, including humans. His discovery and interpretation of the phenomenon of *spontaneous internal desynchronization*[52,53] was a driving

FIGURE 1.18 Jürgen Aschoff (1913–1998). This German physiologist was a leader in the development of the study of circadian rhythms in the twentieth century. (Reprinted from *J. Biol. Rhythms*, 9(3), 187, Copyright 1994 by Sage Publications. With permission of Sage Publications.)

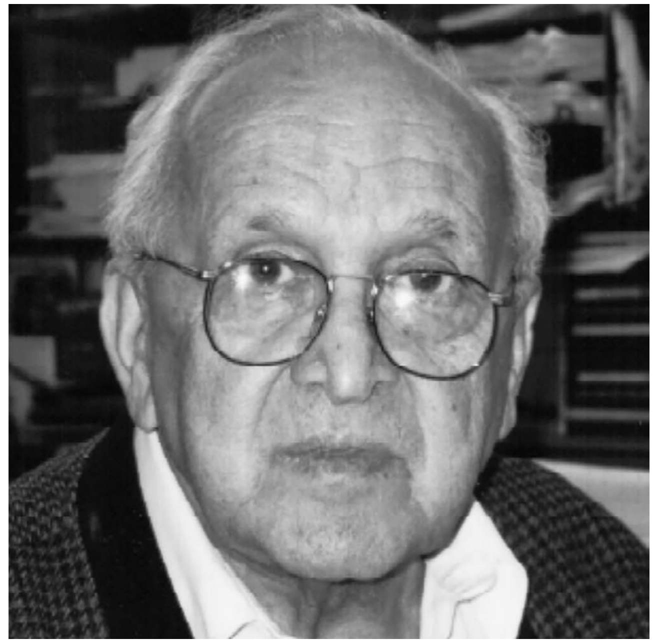

FIGURE 1.19 Franz Halberg (1919–2013). This American physician (originally from Romania) created the terms *circadian* and *chronobiology* and was a life-long advocate of the establishment of chronobiology as a separate discipline. (Photo courtesy of Franz Halberg.)

force in circadian physiology for decades. His thorough and exhaustive reviews of the literature in circadian physiology[54–56] served as invaluable guides to numerous researchers. I met Aschoff in person when he was in his 70s. He showed his age by virtue of his unsurpassed erudition in physiology, but his demeanor reflected the bursting intellectual energy of a 20-year-old. Aschoff died in 1998,[57] but his legacy lives on. Over 30 of his articles are cited in this book.

Franz Halberg (Figure 1.19) was born in Bistrita, Romania, in 1919 and moved to the United States a few years after completing medical school. He spent most of his career at the University of Minnesota. Halberg was the creator of the terms *circadian*[58] and *chronobiology*.[59] A prolific writer, he published over 2500 journal articles and books in circadian physiology, including an introductory booklet on biological rhythms for high-school students.[60] Although the medical applications of circadian physiology were his main concern,[61–63] he conducted a great deal of basic research as well.[64–67] Halberg was still alive and productive when the second edition of this book was written, and I had the chance to consult with him about historical and technical matters. He passed away in 2013.[68]

Colin S. Pittendrigh (Figure 1.20) was born in Whitley Bay, England, in 1919 and moved to the United States as a graduate student. He spent the first 20 years of his faculty career at Princeton University, in New Jersey, and then relocated to Stanford University, in California. A "clock watcher" at heart,[69] he strived to understand how the operation of a physical oscillator could explain circadian rhythmicity in animals. A great deal of our current understanding of the operation of the circadian clock is derived from his work in flies[70,71]

FIGURE 1.20 Colin Pittendrigh (1919–1996). This American biologist was a leader in the development of the study of circadian rhythms in the twentieth century. (Reprinted from Pittendrigh, C.S., *Annu. Rev. Physiol.*, 55, 16, Copyright 1993 by Annual Reviews. With permission. www.annualreviews.org.)

TABLE 1.1
Characteristics of the Two Main Factions in Chronobiology in the Twentieth Century

Faction	Leading Figure	Primary Emphasis	Central Focus	Main Tool	Favored Journal
Clocks	Pittendrigh	Basic	Mechanisms	Actogram	*Journal of Biological Rhythms* (since 1986)
Chronome	Halberg	Applied	Rhythms	Cosinor	*Chronobiologia* (1974–1994)

and rodents.[72–75] I met Pittendrigh in person very late in his life, but I was impressed by his ability to skillfully balance broad biological principles with the detailed experimental dissection of circadian rhythms. He died in 1996,[76] but his contribution to circadian physiology is everlasting, as will become evident in Chapter 7.

The personal and professional interactions between the three forefathers (and their offsprings) were not as cordial and productive as one might have expected. Aschoff did recognize both Halberg's leading role in the development of circadian physiology[6] and Pittendrigh's insights into mechanisms of circadian organization.[55] Pittendrigh acknowledged some of Halberg's contributions[69] and credited Aschoff with important discoveries.[74] On his turn, Halberg recognized the contributions of both Aschoff and Pittendrigh.[77] However, a great divide characterized the field during the second half of the twentieth century. Researchers were divided into two factions that may be referred to as the *clocks* faction and the *chronome* faction. As shown in Table 1.1, the clocks faction was headed by Pittendrigh and concerned itself mainly with the mechanisms of biological timing, whereas the chronome faction (so named because of the proposition that the temporal aspect of biological organization is as encompassing as the genome) was headed by Halberg and concerned itself mainly with the description of rhythmic processes and their relevance to medical application. Aschoff stayed neutral and interacted with both factions. The two factions avoided direct confrontation by holding separate scientific meetings, publishing their papers in separate journals, and generally ignoring each other. Although mutual criticisms were rarely put in print,[78,79] the animosity was clearly revealed by sociologists who looked at the "disciplinary stake" of chronobiology.[80] As a corollary, a textbook published by eminent members of the clocks faction in 2004 presented Pittendrigh and Aschoff as the "founders of chronobiology" with no mention of Halberg. This is especially noteworthy because the book was entitled *Chronobiology*,[12] and it was Halberg who created the term[59] and who forcefully promoted the creation of the new discipline against Pittendrigh's objections.[80]

I should hasten to point out that antagonisms are not peculiar to circadian physiology—or to science more generally. In the musical arts, for instance, the renowned classical composer and conductor Rimsky-Korsakov had this to say about the no-less renowned Ludwig van Beethoven: "His music abounds in countless leonine leaps of orchestral imagination, but his technique, viewed in detail, remains much inferior to his titanic conception."[81] In plain words: "Beethoven is a bad composer!" Needless to say, I and millions of others beg to differ. In any event, small but sincere attempts at reconciliation of the two factions were made over the years. A conference held at the Cold Spring Harbor Laboratory (in Long Island, New York) in 1960 had already brought together Bünning, Aschoff, Halberg, Pittendrigh, and others under one roof,[82] although the division of the factions had not been yet strongly established at that time. Thirty-five years later, in 1995, a conference was organized at Dartmouth Medical School by members of the clocks faction (Figure 1.21). Although most participants were members of the clocks faction, members of the chronome faction were welcomed as well. A few years later, in 1999, an eclectic group of circadian physiologists organized a congress sponsored by nine different professional organizations dedicated to the study of biological rhythms. Participants in this congress—held in Washington, DC (Figure 1.22)—included basic researchers as well as medical practitioners and provided the opportunity for the exchange of ideas between individuals with quite different professional interests. After the turn of the century, in 2001, a World Federation of Societies for Chronobiology was established, bringing together 13 professional associations with diverse interests related to biological rhythms. The federation held its first congress in 2003.[83]

As for the merits of the antagonism between the two factions, something more must be said. Members of the chronome faction often felt that the clocks faction wasted time on esoteric questions instead of addressing important real-life issues. On the other side of the court, members of the clocks faction felt that the chronome faction conducted sloppy research that failed to address the intricacies of the biological clock. Because each faction judged the other by its own values, it was difficult to reach a consensus. Fortunately, members of both factions agreed that peer recognition of one's work is an objective measure of professional achievement. The extent of a researcher's *peer recognition* can be estimated by the number of times that his/her work is cited in publications by other researchers. I used the *Science Citation Index* (produced by Thomson Reuters, in New York) and truncated the search in August 2004 to avoid unfairly favoring Halberg, who lived longer than Aschoff and Pittendrigh. I found that Halberg had 9200 citations, whereas the figures were 8900 and 6800 for Aschoff and Pittendrigh, respectively. Although Halberg had more total citations than Pittendrigh, he had fewer citations per published article (11 as compared to 42), which means that he was cited more often than Pittendrigh was, but his articles were not individually considered as important as Pittendrigh's. The fact that Pittendrigh's individual articles were considered to be more important may reflect his focus on specific topics. Not a man to be content with short stories,