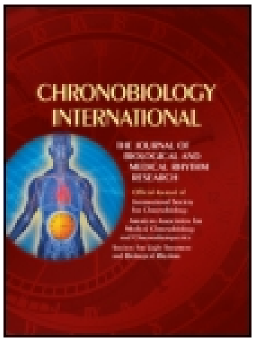

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DISCOVERIES OF RHYTHMS IN HUMAN BIOLOGICAL FUNCTIONS: A HISTORICAL REVIEW

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REVIEW PAPER

DISCOVERIES OF RHYTHMS IN HUMAN BIOLOGICAL FUNCTIONS: A HISTORICAL REVIEW

Björn Lemmer

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Though there are very early and ancient observations on the daily variation in physiological and pathophysiological functions (e.g., bronchial asthma), more detailed and scientific reports were not published until the beginning of the 17th century. The aim of this review is to bring those reports to the attention of researchers of chronobiology and chronopharmacology. The ancient books and their contents, which constitute the basis for this review, are part of the personal library collection of the author; numerous observations and reports on biologic rhythms in man are presented here for the first time. The intent of this review is to demonstrate that the fields of chronobiology and chronopharmacology are not only a new and modern branch of science, but that it stands on the shoulders of wonderful and insightful observations and explanations made by our scientific forefathers. It is the hope that the reader will enjoy the richness of the ancient reports that contribute to our present knowledge achieved through astute early biologic rhythm research. (Author correspondence: bjoern.lemmer@pharmtox.uni-heidelberg.de)

Keywords History of science, Biological rhythms, Chronobiology, Chronopharmacology

BACKGROUND

The field of chronobiology has advanced greatly in recent years, achieving important breakthroughs in research in nearly all areas and in all species. Clock genes have been detected, and the understanding of their regulatory machinery has greatly improved (Brunner et al., 2008; Dardente & Cermakian, 2007; Hastings et al., 2008; Menaker, 2007; Roenneberg et al., 2008; Takahashi et al., 2008). We now have much better insight into the importance of biological rhythms to life and survival

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of single cells, plants, and animals. In man, observations of biological rhythms in health and disease have impacted medicine, in terms of both patient diagnostics and therapy (Lemmer, 2006; Levi & Schibler, 2007; Redfern & Lemmer, 1997; Reinberg & Halberg, 1971; Reinberg & Smolensky, 1983; Smolensky & Peppas, 2007). However, one must keep in mind that the scientists of today are standing on the shoulders of gifted predecessors who in the distant past described wonderful and detailed observations of biological rhythms.

This review presents various early observations of biologic rhythms in human beings that contribute to their translational applications to medicine and pharmacotherapeutics, primarily during the past 400 years, although many of the early discoveries were published in the 18th and 19th centuries. This review is somewhat subjective, and perhaps incomplete, in that it is based on books that were (sometimes) first detected and added to the author's personal library. To emphasize the historical aspects of chronobiology, copies of the original cover and pages of these books that describe important observations are reproduced here in the original language (i.e., Latin, French, German, and English). Nevertheless, relevant non-English passages of the text that are pertinent to chronobiology are translated into English. This review concentrates on important early discoveries of human biological rhythms and concepts, with special reference to as yet unknown ones. This review does not seek to be complete, but informative regarding a set of considered scientific domains. The reader is reminded that other historical chronobiology reviews, outside the scope of this one, have been published, such as the one by Sweeney (1987) and Cumming and Wagner (1968) on plants and by Dunlop et al. (2004) on various species.

This review is also intended to honor early biological rhythm researchers and the great contributions they made to the field of chronobiology. As a sign of appreciation, photographs taken at the Third and Fourth Conferences (see Figures 1 and 2) of the International Society for Biologic Rhythm Research, which were held in Hamburg in 1949 and in Basel, Switzerland, in 1953, are presented (Holmgren et al., 1953; Menzel et al., 1955). I am thankful to Alain Reinberg, who gifted these conference books and photographs to me.

Several noted chronobiologists are shown in the two figures. Jürgen Aschoff (1913–1998) is considered one of the fathers of chronobiology. He was director of the Max-Planck-Intitute in Ehrlich-Andechs near Munich and conducted biological rhythm research both on animals and humans, including under free-running conditions in his bunker experiments. He coined the term *zeitgeber* and developed many concepts of great importance to the field. Franz Halberg (*1919) is another one of the founders of chronobiology. He established the Chronobiology Laboratories at the University of Minnesota and is credited with introducing the

FIGURE 1 3rd Conference of the International Society for Biologic Rhythm Research, Hamburg, 1949 (Holmgren et al., 1953).

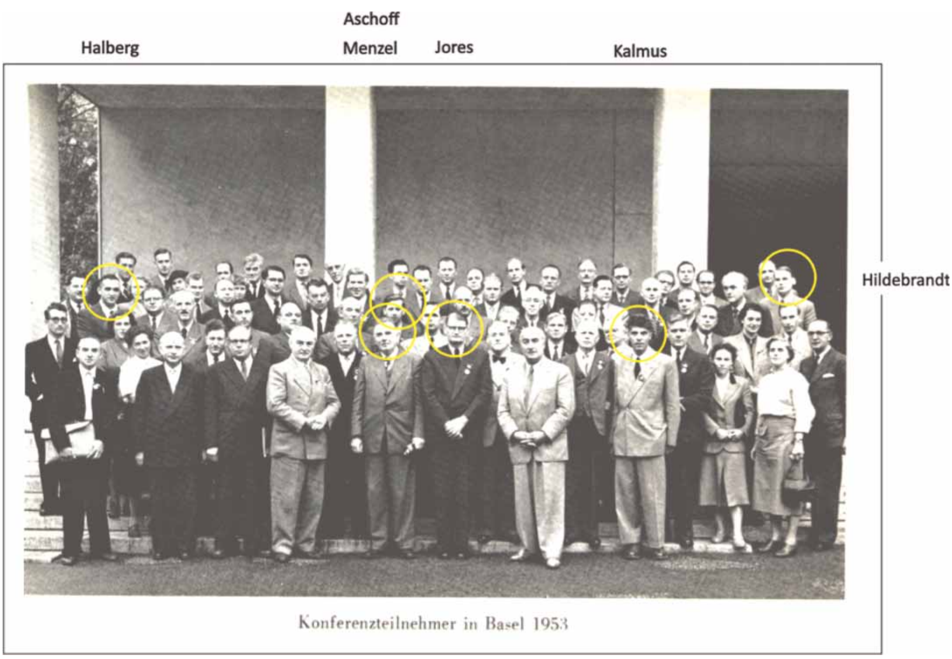


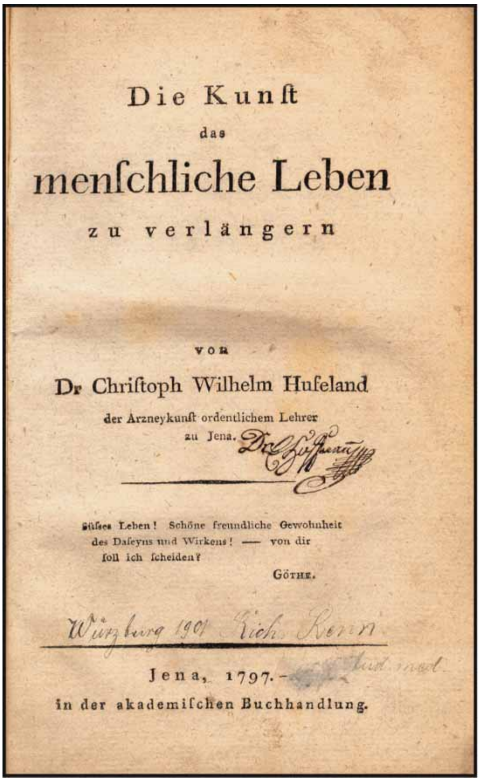
FIGURE 2 4th Conference of the International Society for Biologic Rhythm Research, Basel, 1953 (Menzel et al., 1955). The following illustrious chronobiologists can be identified in the photograph: F. Halberg, J. Aschoff, W. Menzel, A. Jores, H. Kalmus, and G. Hildebrandt.

term *circadian* into the scientific language. The physician Arthur Jores (1901–1982) was a professor of medicine at the University of Hamburg. He made important contributions to the field of rhythms in kidney function, pain perception, and many other areas of medical chronobiology. Hans Kalmus (1906–1988), University College (London), was a biologist who studied the rhythmic behavior of bees, drosophila, and other animal species as well as genetic responses to the seasons of the year and hours of the day. Werner Menzel (1908–1998) was a physician in Hamburg who made a number of significant contributions to the field of clinical chronobiology. Gunther Hildebrandt (1924–1999) was a professor at the University of Giessen; his main scientific interest was the introduction of chronobiology into medicine. He researched the chronobiology of many topics, including balneology, pain perception, and lung and cardiac function. Although not shown in the photograph, the botanist Erwin Bünning (1906–1990) of the University of Tübingen also attended the 1955 conference. He is considered to be one of the founding fathers of chronobiology; he and Jürgen Aschoff are credited with the developing the early concept of the internal clock.

INTRODUCTION

Living organisms are continuously influenced by external stimuli, many of which exhibit cyclic patterns. Daily and seasonal environmental patterns of light (resulting from the regular rotation of the earth around its central axis), food availability, and temperature are predictable, and animals, including humans, possess the ability to anticipate these cyclic environmental events by periodic and predictable changes in internal conditions. These rhythmic patterns of anticipation have clear advantages and survival value. Indeed, rhythmicity is the most ubiquitous feature of nature. Rhythms are found from simple unicellular to complex multicellular organisms—in plants, animals, and man. The frequencies of human biological rhythms cover nearly every division of time: oscillations of one per second (e.g., in the electroencephalogram), one per several seconds (e.g., respiratory rhythm, heart rate), one within 24 h (e.g., circadian rhythms), up to one per year (e.g., circannual rhythms). All such types of rhythms were first observed and reported centuries ago.

General descriptions as well as detailed measurements of human biological rhtythms can be found in many ancient texts. One very famous report, *Die Kunst das menschliche Leben zu verlängern* (see Figure 3), was published more than 200 years ago by a teacher in pharmacology at the University of Jena—Christoph Wilhelm Hufeland, who was also the medical doctor of J.W. von Goethe (Hufeland, 1797). He wrote, "Due to the regular rotation of our planet there is a 24-hour period transmitted to all inhabitants on earth. . .and in all kinds of diseases this regular period


Die Kunst
das
menschliche Leben
zu verlängern

von
Dr Christoph Wilhelm Hufeland
der Arzneykunst ordentlichem Lehrer
zu Jena.

Süsses Leben! Schöne freundliche Gewohnheit
des Daseyns und Wirkens! — von dir
soll ich scheiden?
Göthe.

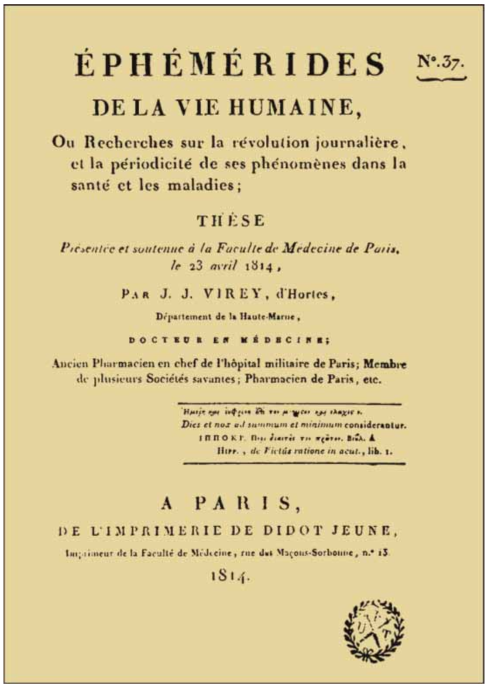
Jena, 1797.
in der akademischen Buchhandlung.

Die 24stündige Periode, welche durch die regelmäßige Umdrehung unseres Erdkörpers auch allen seinen Bewohnern mitgetheilt wird, zeichnet sich besonders in der physischen Oekonomie des Menschen aus. In allen Krankheiten äußert sich diese regelmäßige Periode, und alle so wunderbar pünktlichen Termine in unserer physischen Geschichte werden im Grunde durch diese einzelne 24stündige Periode bestimmt. Sie ist gleichsam die Einheit der Natur-Chronologie.

FIGURE 3 Hufeland *Die Kunst das menschliche Leben zu verlängern*, Jena, akademische Buchhandlung, 1st ed., pp. 550–551 (Hufeland, 1797).

can be found again, and this 24-hour period determines the wonderful timing of all our bodily functions. This period can be called the unit of the chronology of nature" (Hufeland, 1797, pp. 550–551).

Another important early publication on the importance of medical chronobiology and biologic rhythm research in health and disease is the doctoral thesis of Julien-Joseph Virey, *Éphémérides de la Vie Humaine, ou Recherches sur la révolution journalière, et la périodicité de ses phénomènes dans la santé et les maladies* (see Figure 4), presented to the Medical Faculty of Paris in 1814 (Virey, 1814). He described not only rhythmic observations, including the differential benefit of the timed dosing of medications such as opium, but gave consideration to underlying mechanisms. Virey also referred to Thomas Sydenham (1624–1689), who is recognized as one of the founders of clinical medicine and epidemiology (Sydenham, 1697). Sydenham recommended administering the medication *parégorique opiatique* (p. 37) in the evening to optimize its effect in reducing intestinal pain. In order to explain his rhythmic observations, Virey (1814, p. 33) suggested "*une sorte d'horloge vivante, montée par la nature, entraînée par le mouvement rapide du soleil*" ("a kind of living clock, made by nature, and



ÉPHÉMÉRIDES N°.37.

DE LA VIE HUMAINE,

Ou Recherches sur la révolution journalière, et la périodicité de ses phénomènes dans la santé et les maladies;

THÈSE

Présentée et soutenue à la Faculté de Médecine de Paris, le 23 avril 1814,

PAR J. J. VIREY, d'Hortes,

Département de la Haute-Marne,

DOCTEUR EN MÉDECINE;

Ancien Pharmacien en chef de l'hôpital militaire de Paris; Membre de plusieurs Sociétés savantes; Pharmacien de Paris, etc.

[illegible]
Dies et nox ad summum et minimum considerantur.
[illegible]
Hipp., *de Victûs ratione in acut.*, lib. 1.

A PARIS,

DE L'IMPRIMERIE DE DIDOT JEUNE,

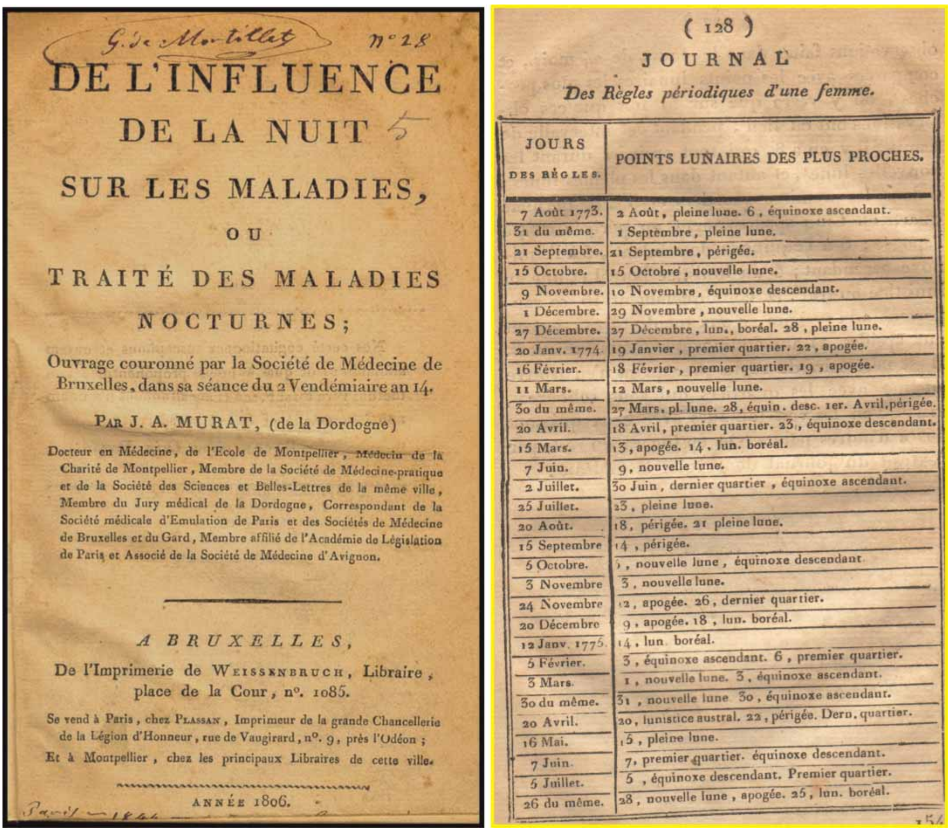
Imprimeur de la Faculté de Médecine, rue des Maçons-Sorbonne, n.° 13.

1814.

FIGURE 4 Thesis of Julien-Joseph Virey presented to the Medical Faculty of Paris in 1814 (Virey, 1814). Appreciation is acknowledged to A. Reinberg for providing the author a copy of this thesis.

entrained by the rapid movement of the sun"). Virey is also considered to be the first chronopharmacologist based on his observations and concepts as embodied by his statement: "*Tout médicament d'ailleurs n'est pas également bien indiqué à toute heure*" ("All medicines are not equally indicated effective given at different hours of the day") (Virey, 1814, p. 37). A thorough description of Virey's achievements and contributions to chronobiology can be found in Reinberg et al. (2001).

Eight years before Virey presented his thesis, the French physician J.A. Murat, of the Medical School of Montpellier (France), published his outstanding book *De L'Influence de la Nuit sur les Maladies ou Traité des Maladies Nocturne* (Murat, 1806). The most evident motivation for his observations is the constant and periodic movement of the earth around its axis, resulting in a period of about 24 h, and the elliptic rotation around the sun with a duration of 365 days, 5 h, and 49 min: "*Le globe de la terre a deux mouvemens constant et périodiques. L'un diurne, par lequel it tourne autour de son axe, dont la période est de 24 heures, ce qui forme le jour, . . . ; l'autre annuel, et autour du soleil, se fait dans un orb elliptique durant l'espace de 365 jours, 5 heures, 49 minutes*" (Murat, 1806, pp. 102, 124). Murat referred the work of Sanctorius, Medicus, Floyer, de Bordeu, Hellwig, and Zimmermann, who are also cited in this review. Murat described periodic phenomena in physiology and in health and disease: "*La phénomène périodique le plus remarquable parmi les fonctions physiologiques, et qui coincide le mieux avec les succession constante du jour et de la nuit ... c'est le retour alternatif du sommeil et de la veille. Cette fonction n'appartient pas aux phénomènes du périodisme physique, mais elle s'en rapproche, si la cause qui fait naitre ne réside point en nous:Il existe donc une cause, qui oblige le principe de vie de répéter les actes alternatifs de sommeil et de la veille*" (Murat, 1806, p. 124). Furthermore, he summarized nearly all observations of that time made on nocturnal diseases. He was curious to learn the basic principle of life that repeats alternations, such as sleep and wakefulness: "*Dans tous les temps l'homme a voulu pénétrer la raison des choses*" (p. 102). Murat also was the first to show that the menstrual cycle, based on data collected between 1773–1775 (for more than two years) from one woman by a physician, is independent of the lunar cycle (see Figure 5). At the end of the 20th century—that is, at the time of women's liberation movement—


DE L'INFLUENCE
DE LA NUIT
SUR LES MALADIES,
OU
TRAITÉ DES MALADIES
NOCTURNES;
Ouvrage couronné par la Société de Médecine de Bruxelles, dans sa séance du 2 Vendémiaire an 14.
PAR J. A. MURAT, (de la Dordogne)
Docteur en Médecine, de l'Ecole de Montpellier, Médecin de la Charité de Montpellier, Membre de la Société de Médecine-pratique et de la Société des Sciences et Belles-Lettres de la même ville, Membre du Jury médical de la Dordogne, Correspondant de la Société médicale d'Emulation de Paris et des Sociétés de Médecine de Bruxelles et du Gard, Membre affilié de l'Académie de Législation de Paris et Associé de la Société de Médecine d'Avignon.
A BRUXELLES,
De l'Imprimerie de WEISSENBRUCH, Libraire, place de la Cour, n°. 1085.
Se vend à Paris, chez PLASSAN, Imprimeur de la grande Chancellerie de la Légion d'Honneur, rue de Vaugirard, n°. 9, près l'Odéon; Et à Montpellier, chez les principaux Libraires de cette ville.
ANNÉE 1806.

(128)
JOURNAL
Des Règles périodiques d'une femme.

JOURS DES RÈGLES.	POINTS LUNAIRES DES PLUS PROCHES.
7 Août 1773.	2 Août, pleine lune. 6, équinoxe ascendant.
31 du même.	1 Septembre, pleine lune.
21 Septembre.	21 Septembre, périgée.
15 Octobre.	15 Octobre, nouvelle lune.
9 Novembre.	10 Novembre, équinoxe descendant.
1 Décembre.	29 Novembre, nouvelle lune.
27 Décembre.	27 Décembre, lun., boréal. 28, pleine lune.
20 Janv. 1774	19 Janvier, premier quartier. 22, apogée.
16 Février.	18 Février, premier quartier. 19, apogée.
11 Mars.	12 Mars, nouvelle lune.
30 du même.	27 Mars, pl. lune. 28, équin. desc. 1er. Avril, périgée.
20 Avril.	18 Avril, premier quartier. 23, équinoxe descendant.
15 Mars.	13, apogée. 14. lun. boréal.
7 Juin.	9, nouvelle lune.
2 Juillet.	30 Juin, dernier quartier, équinoxe ascendant.
25 Juillet.	23, pleine lune.
20 Août.	18, périgée. 21 pleine lune.
15 Septembre	14, périgée.
5 Octobre.	[illegible], nouvelle lune, équinoxe descendant
3 Novembre	3, nouvelle lune.
24 Novembre	12, apogée. 26, dernier quartier.
20 Décembre	9, apogée. 18, lun. boréal.
12 Janv. 1775.	14, lun. boréal.
5 Février.	3, équinoxe ascendant. 6, premier quartier.
3 Mars.	1, nouvelle lune. 3, équinoxe ascendant.
30 du même.	31, nouvelle lune 30, équinoxe ascendant.
20 Avril.	20, lunistice austral. 22, périgée. Dern. quartier.
16 Mai.	15, pleine lune.
7 Juin.	7, premier quartier. équinoxe descendant.
5 Juillet.	5, équinoxe descendant. Premier quartier.
26 du même.	28, nouvelle lune, apogée. 25, lun. boréal.

FIGURE 5 Murat's book, *De L'Influence de la Nuit sur les Maladies ou Traité des Maladies Nocturne*, on periodic phenomena in health and disease. The table (p. 128) shows data on the monthly ocurrence of the menstrual cycle in relation to the cycle of the moon in one woman. Murat found no corrrelation between the two cyclic phenomena (Murat, 1806).

this idea was very popular with the public. Obviously, the discovery of Murat was unknown.

A great number of historical reports refer to observations of periodicities in specific diseases. The following sections review these observations, and at the end of each section, the impact of these early discoveries on modern medicine is briefly highlighted.

BRONCHIAL ASTHMA

Asthma is a chronic inflammatory disease of the airways characterized by hyperresponsivness to a great variety of substances and stimuli. Nighttime worsening of asthma has long been recognized—at least since the second century, based on the work of Soranus from Ephesus, who practiced medicine in Alexandria and later in Rome. The Roman physician Caelius Aurelianus in the fifth century was one of the first to report in a chapter of his book, *De Morbis Acutis & Chronicis*, on the daily variation in asthma attacks: "*De Suspirio, sive Anhelitu, quem Graeci Asthma vocant – Gravat autem atque premit haec passio magis mulieribus viros, & juvenibus senes, atque pueros, & durioribus natura corporis teneriora, hyberno, atque nocte magis, quam die vel aestate*" ("On the heavy breath and wheeze which is called asthma by the Greeks, this disease is a burden, and men suffer more than women, and the elderly more than the young ... during winter and at night more than during the day or in spring") (Aurelianus, 1722, p. 429). Caelius Aurelianus is considered by most historians to have been the greatest Greco-Roman physician after Galen. Caelius Aurelianus probably practiced and taught in Rome and is today ranked second only to the physician Celsus as a Latin medical writer. His most famous work, *De Morbis Acutis et Chronicis* (Concerning Acute and Chronic Diseases), constitutes a thorough exposition of the classical medical knowledge of the times and was regularly reprinted up to the 18th century (see Figure 6).

Additional early observations and discriptions of nocturnal asthma are known. In 1568, Wirsung (1568) related in his *Arzney Buch* (*Book on Drugs*, see Figure 7) that the symptoms of asthma—a severe wheezing breath—occur between 2 h after midnight until the morning: "§9 *Von schwerem keuchendem Athem: Jedoch etwas einleitung zu geben/seye diß der anfang. Wo dieser kurtzer unnd keuchender Athem/auß zeher Phlegmatischer materi/welche die Brüst erfület kommet/So hast du diß bey volgenden zeichen zu erkennen/daß sich eine schwere/truckende engin des Athmens erzeigt/unnd mehr umb die zeit/wann sich der Schleim bewegt/das ist zwo stund nach Mitternacht biß auff den Morgen*" (Wirsung, 1568, pp. 201–202).

In 1616, Castello Petro Vasco stated in his book chapter, *Tractatus Tertius de Asthmate*, that asthma is a predominantly nocturnal disease ("*atqui Asthmatica dispositio nocturnis horis magis affligit*") that is more severe during winter and at night than during summer and daytime ("*hyberno*

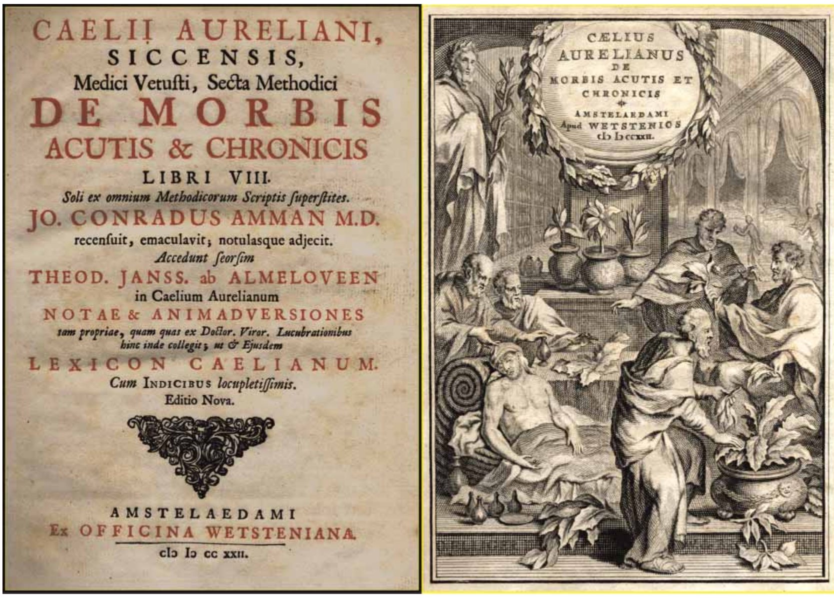

CAELII AURELIANI,
SICCENSIS,
Medici Vetusti, Secta Methodici
DE MORBIS
ACUTIS & CHRONICIS
LIBRI VIII.
Soli ex omnium Methodicorum Scriptis superstites.
JO. CONRADUS AMMAN M.D.
recensuit, emaculavit; notulasque adjecit.
Accedunt seorsim
THEOD. JANSS. ab ALMELOVEEN
in Caelium Aurelianum
NOTAE & ANIMADVERSIONES
tam propriae, quam quas ex Doctor. Viror. Lucubrationibus hinc inde collegit; ut & Ejusdem
LEXICON CAELIANUM.
Cum Indicibus *locupletissimis.*
Editio Nova.
AMSTELAEDAMI
Ex OFFICINA WETSTENIANA.
CIϽ IϽ CC XXII.

FIGURE 6 Caelius Aurelianus lived in the 5[th] century. His textbook, *De Morbis Acutis et Chronicis*, describes the nocturnal occurrence of asthma. Editio nova. Amsterdam, Wetsten (Aurelianus, 1722).

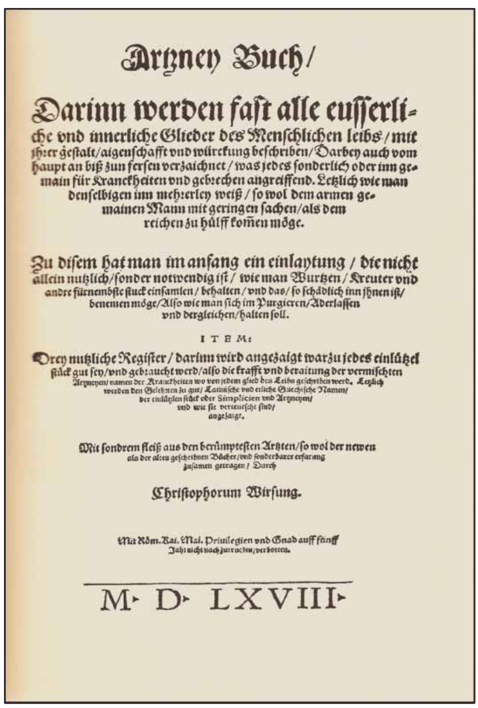

Artzney Buch/
Darinn werden fast alle eusserliche vnd innerliche Glieder des Menschlichen leibs/ mit jhrer gestalt/aigenschafft vnd würckung beschriben/ Darbey auch vom haupt an biß zun fersen verzaichnet/ was jedes sonderlich oder inn gemain für Kranckheiten vnd gebrechen angreiffend. Letzlich wie man denselbigen im mehrerley weiß/ so wol dem armen gemainen Mann mit geringen sachen/als dem reichen zu hülff komen möge.
Zu disem hat man im anfang ein einlaytung / die nicht allein nutzlich/sonder notwendig ist/ wie man Wurtzen/ Kreuter vnd andre fürnembste stuck einsamlen / behalten / vnd das/ so schädlich inn jhnen ist/ benemen möge/ Also wie man sich im Purgieren/ Aderlassen vnd dergleichen/ halten soll.
ITEM:
Drey nutzliche Register/ darinn wird angezaigt warzu jedes einlützel stück gut sey/ vnd gebraucht werd/ also die krafft vnd beraitung der vermischten Artzneyen/ namen der Kranckheiten wo von jedem glied des Leibs geschriben werd. Letzlich werden den Gelehrten zu gut/ Latinische vnd etliche Griechische Namen/ der einlützlen stück oder Simplicien vnd Artzneyen/ vnd wie sie verteutscht sind/ angezaigt.
Mit sondrem fleiß aus den berümptesten Artzten/ so wol der newen als der alten geschribnen Bücher/ vnd sonderbarer erfarung zusamen getragen/ Durch
Christophorum Wirsung.
Mit Röm. Kai. Mai. Privilegien vnd Gnad auff fünff Jahr nicht nach zutrucken/ verbotten.
M. D. LXVIII.

FIGURE 7 Front page of Wirsung's *Arzney Buch* (Wirsung, 1568), in which asthma symptoms are described as occurring at night.

tempore, atque nocte magis quam die, vel Aestate") (Vasco, 1616, pp. 253–254). He also used the term *asthma noctu* (nocturnal asthma) to characterize the asthmatic disposition that predominates during the night (see Figure 8).

In the 18th century, the English physician Sir John Floyer (1639–1734), who suffered from asthma for about 30 yrs, remarked in his book, *A Treatise of the Asthma* (1698), "*I have observed the fit always to happen after sleep in the night*" (Floyer, 1698, 1761, p. 102). Floyer decribed his own symptoms in great detail, and how they were influenced by the environment and seasons and by treatment. He writes, "*I cannot remember the first occasion of my asthma, but I have been told that it was a cold when I first went to school. As my asthma was not hereditary from my ancestors, so I thank God neither of my two sons are inclined to it, who are now past the age when it seized me*" (p. 20). The first French edition of his book is shown in Figure 9.

Coste (1767) described in his book, *Traité des Maladies du Poumon*, the asthmatic attack as an obstruction of the small bronchi ("*les petits extrémités des bronches resteront obstruées*") (see Figure 10). Interestingly, he also noted the inflammation of the bronchial membranes in asthma: "*S'il est arrivé á la suite d'une légère inflammation de la membrane don't trachée artère & les bronches du Poumon*" (Coste, 1767, p. 43). This observation was not fully appreciated

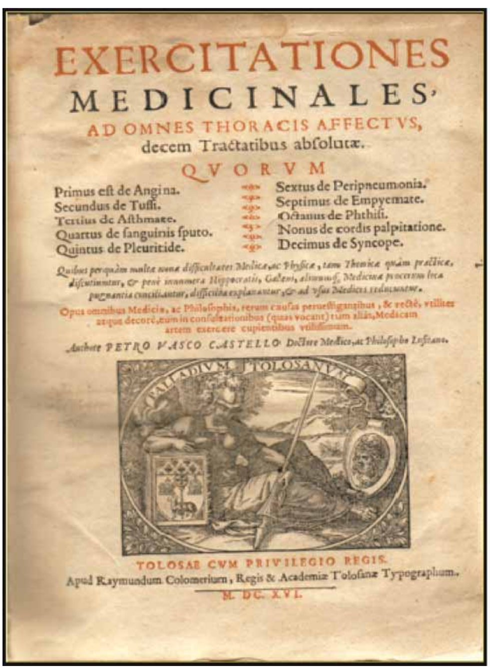
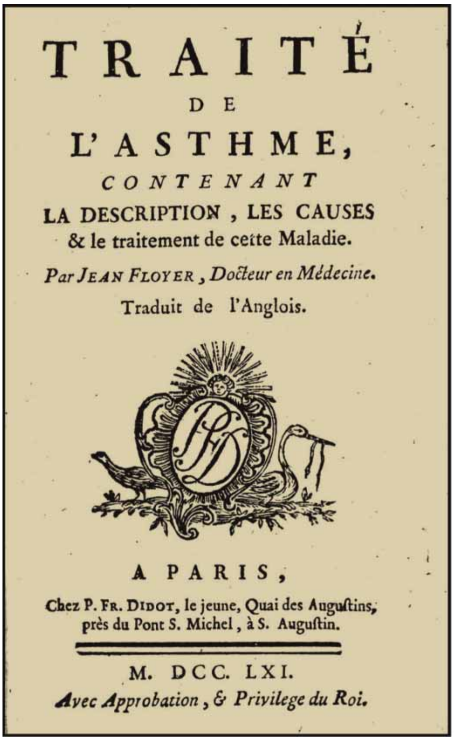


FIGURE 8 Textbook of Castello Petro Vasco, *Exercitationes Medicinales ad Omnes Thoracis Affectus, decem Tractatibus Absoluta*. Raymon Colomerius (Raymundum Colomerium, Regis & Academiae Tolosanae), Toulouse (Vasco, 1616).


TRAITÉ
DE
L'ASTHME,
CONTENANT
LA DESCRIPTION, LES CAUSES
& le traitement de cette Maladie.
Par JEAN FLOYER, *Docteur en Médecine.*
Traduit de l'Anglois.

A PARIS,
Chez P. FR. DIDOT, le jeune, Quai des Augustins,
près du Pont S. Michel, à S. Augustin.

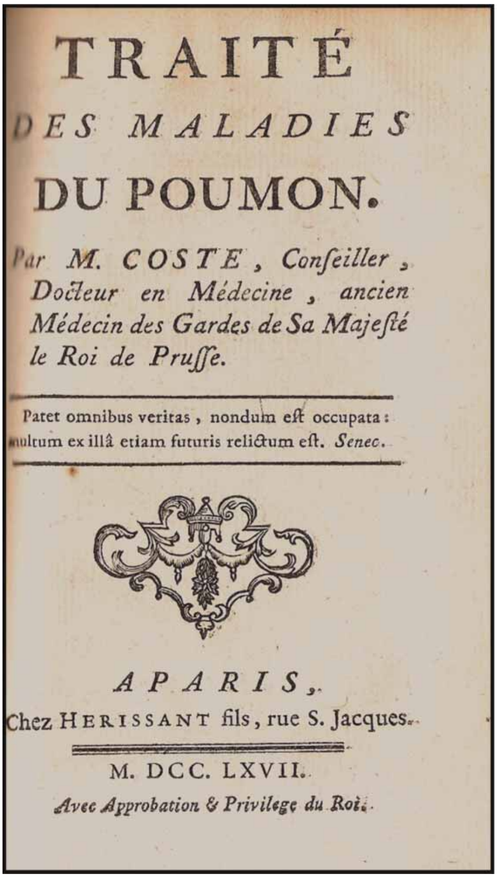
M. DCC. LXI.
Avec Approbation, & Privilege du Roi.

J'ai observé que l'accès arrive toujours après le sommeil & dans la nuit, lorsque les nerfs sont remplis d'épris flatueux, & que la chaleur du lit a raféfié les esprits & les humeur.

FIGURE 9 First French edition of Floyer's work on asthma, *Traité de l'Asthme*. PF Didot le jeune, Paris (Floyer, 1761).

until the end of the 20th century, as documented by the recommendation of national and international clinical disease guidelines that antiinflammatory medications, such as topical corticosteroids, be a primary means of managing bronchial asthma (Expert-Panel-Report, 2007).

Later on, Armand Trousseau (1801–1867), who like Floyer also suffered from nocturnal asthma ("*Ainsi pour moi, qui depuis lengtemps en suis affecté, mes attaques me prenaient autrefois vers trois heures du matin*") (Trousseau, 1868, p. 441) and allergic rhinitis, published his excellent observations in *Clinique Médicale de l'Hotel-Dieu de Paris*. Of course, Trousseau's insight preceded the discovery of allergy, allergens, and underlying immunological processes (Trousseau, 1868). Trousseau was a physician in the Hôtel-Dieu awarded the chair of therapy and pharmacology of the Paris Medical Faculty. Trousseau suspected his cab driver was stealing oats from his horses, which motivated him to go to the horse stable during the night to check the number of bags. Trousseau found that when he manipulated the bags of oats to feed the horses at night, the inhaled dust triggered an asthma attack (see Figure 11). He also conceived and described allergic rhinitis as asthma of the nose ("*Le coryza, mais un coryza spéciale, peut être l'expression de la maladie et en constituer*



TRAITÉ
DES MALADIES
DU POUMON.

Par M. COSTE, Conseiller, Docteur en Médecine, ancien Médecin des Gardes de Sa Majesté le Roi de Prusse.

Patet omnibus veritas, nondum est occupata: multum ex illâ etiam futuris relictum est. *Senec.*

A PARIS,
Chez HERISSANT fils, rue S. Jacques.
M. DCC. LXVII.
Avec Approbation & Privilege du Roi.

De l'Asthme.

S'il est arrivé à la suite d'unelégère inflammation de la membrane ...

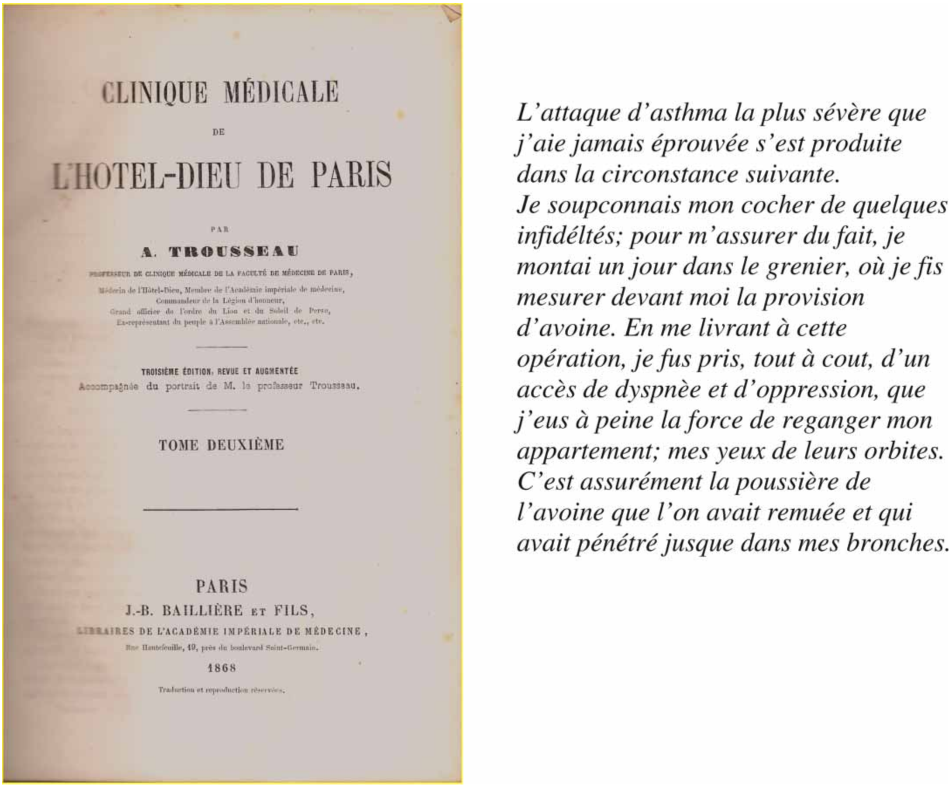
.. les petits extrémités des bronches resteront obstruées ...

FIGURE 10 Coste's *Traité des Maladies du Poumon* (Coste, 1767).

la seul manifestation") (Trousseau, 1868, p. 440). Furthermore, he ordered inhalation of an anticholinergic compound (*Datura stramonium*) as a remedy for asthma (Trousseau, 1868, pp. 444, 468). It is of interest that anticholinergics still are used today to manage this medical condition (Expert-Panel-Report, 2007).

Finally, it should be mentioned the French physician, Murat, also recognized asthma to be an nighttime disorder, "nocturnal asthma" (*Nocturne simple: est paticulière à l'asthma.*) (Murat, 1806; pp. 72, 120).

The father of experimental pharmacology, Rudolf Buchheim (1820–1879) of the German Dorpat University (now Tartu, Estonia), recommended in his Textbook on Pharmacology, *Lehrbuch der Arzneimittellehre*, published in the middle of the 19th century, to use atropin extracts (*Belladonnablätter*) to treat periodic asthma: "frequently one is allowed to smoke leaves from Jimson weed or deadly nightschade. . .which seems to be of special value in periodic asthma"(Buchheim, 1853–1856, p. 527; see Figure 12). Synthetic anticholinergics are nowadays also mediciations



CLINIQUE MÉDICALE

DE

L'HOTEL-DIEU DE PARIS

PAR

A. TROUSSEAU

TROISIÈME ÉDITION, REVUE ET AUGMENTÉE

Accompagnée du portrait de M. le professeur Trousseau.

TOME DEUXIÈME

PARIS

J.-B. BAILLIÈRE ET FILS,

LIBRAIRES DE L'ACADÉMIE IMPÉRIALE DE MÉDECINE,

1868

L'attaque d'asthma la plus sévère que j'aie jamais éprouvée s'est produite dans la circonstance suivante.
Je soupconnais mon cocher de quelques infidéltés; pour m'assurer du fait, je montai un jour dans le grenier, où je fis mesurer devant moi la provision d'avoine. En me livrant à cette opération, je fus pris, tout à cout, d'un accès de dyspnèe et d'oppression, que j'eus à peine la force de reganger mon appartement; mes yeux de leurs orbites. C'est assurément la poussière de l'avoine que l'on avait remuée et qui avait pénétré jusque dans mes bronches.

FIGURE 11 Armand Trousseau's book, *Clinique Médicale de l'Hotel-Dieu de Paris*. J.-B. Baillière et fils, Paris 1868, p. 447 (Trousseau, 1868).

of choice in the treatment of asthma and COPD (chronic obstructic pulmonary disease) (Expert-Panel-Report, 2007).

Impact on Modern Medicine

- International (Expert Panel Report) staging of asthma according to rhythm in peak flow, definition of nocturnal asthma;
- Measurement of lung functions during day and night; development of peak flow meters for patient self-monitoring of circadian rhythm in airways status;
- Recommendation of evening dosing of certain asthma medications;
- Recognition that allergic symptoms more severe at night and early morning hours;
- Dosing of medications (antihistamines, etc.) for allergic rhinitis in the evening.

For further discussion of bronchial asthma, please see Expert-Panel-Report (2007) and Smolensky et al. (2007b).

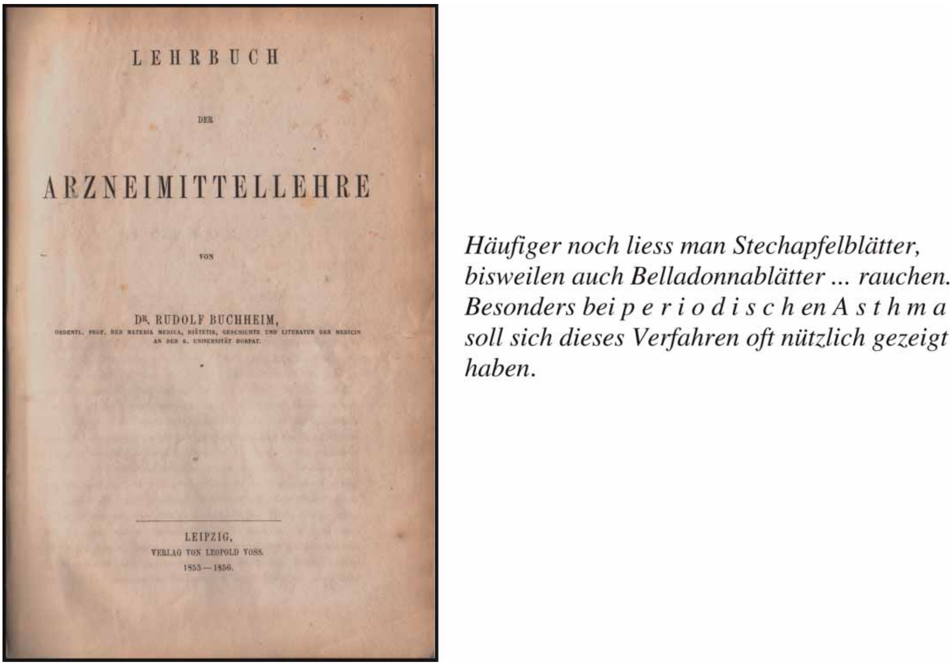


FIGURE 12 Textbook on Pharmacology, *Lehrbuch der Arzneimittellehre*, of R. Buchheim, L. Voss, Leipzig (Buchheim, 1853–1856).

RHYTHMS IN HEART RATE

Heart rate was one of the earliest physiological functions reported not to be constant throughout the 24 h. As early as the beginning of the 17th century, day-night variations in pulse rate (Sanctorius, 1631b; Struthius, 1602; Targiri, 1698) as well as rapid increase on awakening (Struthius, 1602) were described. In the 18th and 19th centuries and the beginning of the 20th century, general observations plus detailed data on daily variations in pulse rate and pulse quality were reported (Autenrieth, 1801; Barthez, 1806; Bordenave, 1787; Falconer, 1797; Hensen, 1900; Hill, 1898; Howell, 1897; Hufeland, 1797; Jellinek, 1900; Knox, 1815; Lemmer, 1989, 1991, 2001, 2004a, 2004b, 2005, 2007a; Reil, 1796; Weysse & Lutz, 1915; Wilhelm, 1806b; Zimmermann, 1793). Joseph Struthius (1510–1568), the physician of the Polish Emperor Sigismund, was apparently the first to correlate the different frequencies and qualities of the pulse through the annotation of music, as recorded in his book, *Ars Sphygmica* (see Figure 13). This idea was used again by Quantz (see below). Struthius also mentioned that variations in pulse rate can differ between men and women, sleep and activity, health and disease, and season (see Figure 13). Thus, Struthius is one of the first outstanding scientists who showed that pulse rate is regulated both by internal and external factors.

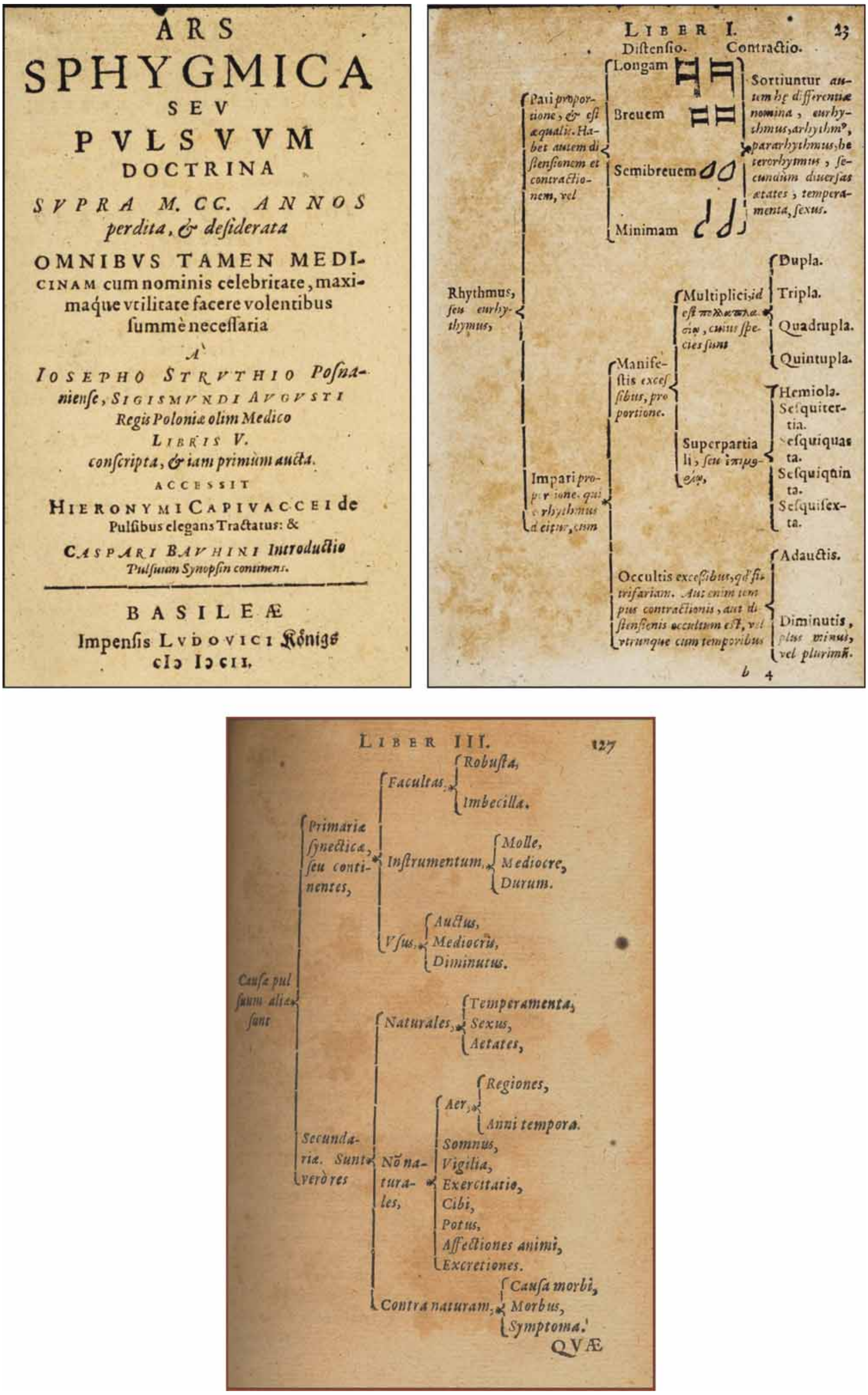


FIGURE 13 First description of a correlation of pulse rate with annotation of music, with mention of the different causes of changes in pulse rate, including season, in Struthius' book, *Ars Sphygmica* (Struthius, 1602).

Johann Struthius was also the first to note that the pulse rate can be influenced by aging (Struthius, 1602) (see Figure 13). Years later, data were presented by many others to verifiy this observation (Autenrieth, 1802; Bordenave, 1787; Falconer, 1797; Hufeland, 1797; Zimmermann, 1793).

In 1767, the famous surgeon and urologist Le Cat (1700–1768) confirmed in his book, *Traité des Sensations et Passions en Général et des Sens en Paticulier*, that music has a great effect on the human soul: *"Ce pouvoir qu'a la musique de remuer l'ame, & par elle toute la machine, la rend très-propre à la santé; et vous consévrez aisément cet effet, si vous avez compris la grande liaison qui est entre ces deux parties de l'homme"* (Le Cat, 1767, p. 286).

Increase in pulse rate and blood pressure at the sight of the doctor, termed *office* or *white-coat effect*, is neither a new nor a recent observation. More than 300 years ago, Targiri reported in his book, *Medicina Compendaria*, that pulse can be modified by internal and external factors, such that even the presence of the doctor can increase the pulse of a patient: "*Ante omnia in scrutanda pulsatione arteriae scientum est, hujusce motum varie accelerandi, minui, imo turbari posse a causis & circumstantiis externis; in quibus minimi momenti non est ipse adspectus & introitus medici, quo saepe aegri vel ad tristitiam vel ad hiliratetem diversimodo disponuntur, quod sane multam excitare in pulsu mutationem potest*" ("First of all, one has to be experienced in studying the pulse, the movement of which can be many-fold increased, reduced, and disturbed due to internal and external reasons. Even the sight of the doctor and his entrance into the office is not of minor importance, since this can result in an increased movement of the pulse") (Targiri, 1698, p. 662; see Figure 14).

A similar observation was described by Hellwig (pseudonym: Valentin Kräutermann) in his book *Curieuser und Vernünftiger Urin-Arzt*: *"Vor allen Dingen stehet aber zu wissen, daß der Puls sich mercklich verändern … könne, wozu nicht wenig Anlaß giebet die Ankunft des Medici, dannenhero der Medicus nicht alsobald beym Eintritt über den Patienten herfahren soll, und den Pulß fühlen, er muß sich erstlich eine Weile niedersetzen, und mit dem Patienten discutiren, und währenden Discurs einmal oder etliche die Ader fühlen"* ("It is important to note that the pulse can vary greatly … a main reason is the advent of the doctor, when he enters the office, he has to sit down at the site of the patient, talk to him, and then he can feel the artery of the patient once or several times") (Hellwig, 1738, p. 134; see Figure 15). This is also the basis for the recommendation found in today's medical guidelines for the office measurement of blood pressure to avert or minimize the risk of the so-called white-coat effect resulting in a diagnosis of (pseudo)hypertension. Théophile de Bordeu (1722–1776), a French physician in Montpellier (France), also described in *Recherches sur le Pouls* the symptoms of what he termed the "pulse of the doctor." He wrote: "In order to estimate the quality of the pulse, it is neccessary to feel the pulse several times; it is an exception that the presence of the doctor does not lead occasionally to some changes which may elevate or increase it: the practitioners never

JOACHIMI TARGIRI
MED. DOCT.
MEDICINA
COMPENDIARIA,
In qua,
Propositis Veterum Sententiis, Nova & verissima artis Medicae Forma ac Ratio breviter & dilucide explicatur.
Lugduni in Batavis,
Apud FREDERICUM HARINGIUM
cIɔ Iɔc xcviii.
1698

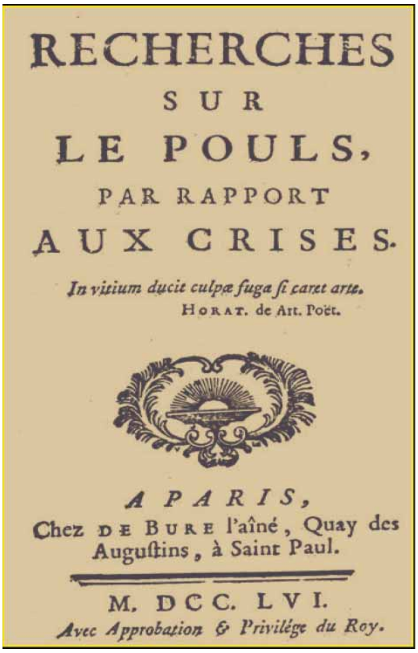
VALENTINI Kräutermanns
Curieuser und vernünfftiger
Urin-Artzt,
Welcher eines Theils lehret und zeiget,
Wie man aus dem Urin nicht allein
die meisten und vornehmsten Kranckheiten des menschlichen Leibes nach gewissen Kunst-Regeln der Medicin gründlich erkennen, sondern auch, wie ein vernünfftiges Judicium davon zu fällen sey;
Andern Theils:
Wie man auch aus dem Puls den Zustand
des Geblütes, die Stärcke und Schwäche der Lebens-Geister, Ab- und Zunahme der Kranckheit ersehen, und das Aderlassen nach denen Complexionen der Menschen, Lauff des Mondes, derer Planeten und Aspecten, mit Nutzen anstellen solle.
Deme noch beygefüget eine curieuse und sehr dienliche
Aderlaß-Tafel.
Nebst nöthigem Register zum Druck befördert.
Dritte Auflage.
Arnstadt und Leipzig,
Verlegts Johann Jacob Beumelburg, 1738.

FIGURE 14 Front pages of the books of Targiri (Targiri, 1698) and Hellwig (pseundonym: Kräutermann) (see Hellwig, 1738) describing the so-called office/white coat effect on patients when assessing heart rate and as also appreciated nowadays when assessing blood pressure (see Lemmer, 1995).

forget to keep in mind the pulse which they call the 'pulse of the doctor'" (de Bordeu, 1756, p. 471; see Figure 15).

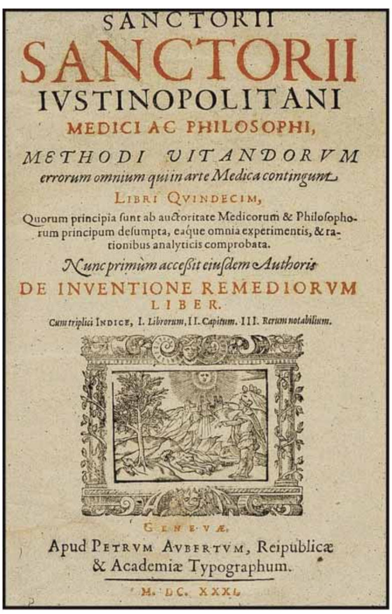
In those times, however, it was difficult to precisely measure the heart rate, as no watches built with minute hands were easily available. Sanctorius Sanctorius (1561–1636), a professor of physiology at the University of Padua, was aware of this problem. He invented a device—the first machine system in medical history—that he called the *pulsilogium* to measure the pulse (Sanctorius, 1631a, 1631b; see Figure 16): "In order to be able to commemorate quickly and excatly my knowledge on the pulse of a patient, I have invented the pulsemeter (pulsilogium), which is possible to measure exactly the beats of the arteries ... and to compare them with the beats of earlier days .... With the help of the pulsemeter, we can monitor at what day and at which hour the pulse deviated in intensity and frequency from its natural state" (Sanctorius, 1631b, p. 289). By modifying the length of the pendulum of the pusilogium, the pulse rate of a patient could be kept for later comparisons.

John Floyer (1649–1734) was also interested in measuring pulse rate. In 1710, he wrote: "I have for many years tried pulses by the minute in



Il fau, en général, pour bien juger de l'état du pouls, le tâter à plusieurs reprises; il est rare que la présence du Médicin n'occasionne d'abord quelque changement dans le pouls, qu'elle ne le rende plus *élevé*, ou plus *serré*: les Praticiens ne perdent jamais du vue le pouls qu'ils appellent *le pouls du Médicin*.
p. 471

FIGURE 15 Front page of the book of Bordeu, *Recherches sur le Pouls*, (de Bordeu, 1756) describing "*pulse of the doctor*" (i.e., office/white-coat effect) (see Lemmer, 1995).



De pusilogii usu.
pro qua cognitione exacte, & cito comparanda instrumentum pulsilogium invenimus in quo motus, & quietes arteria quique poterit exactissime dimetiri, observare, & firma memoria tenere, & inde collationem facere cum pulsibus praeteritum dierum...
ex cuius pulsilogii observatione primo colligimus qualibet die, & hora quantum aegri recedant in crebritate a statu naturali...

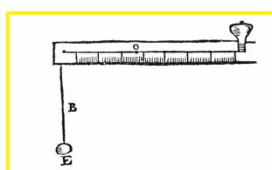


FIGURE 16 Cover page of *Methodi Vitandorum*, description of the *pulsilogium*, a device invented by Sanctorius (1631b) to measure pulse rate; detailed data are given in Sanctorius' book *De Inventione Mediorum* (Sanctorius, 1631a).

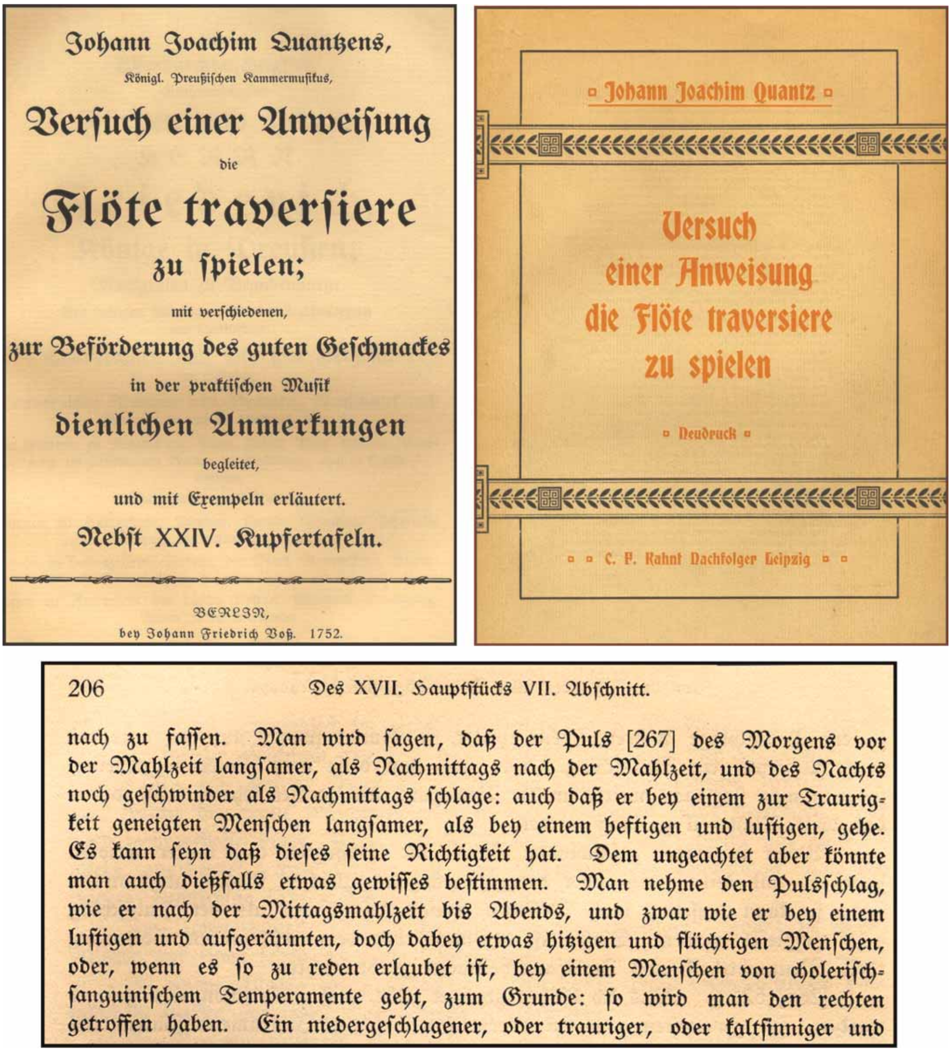
common watches and pendulum clocks and then used the sea-minute glass such as is employed to test the log" (*The Physician's Pulse-Watch; or An Essay to Explain the Old Art of Feeling the Pulse and to Improve It by the Help of a Pulse-Watch* [Floyer, 1707–1710]).

The pulse of a healthy subject as determined in the late afternoon was even proposed as an easily available metronome for use by musicians playing the flute (Quantz, 1752, 1906). Johann Joachim Quantz (1697–1773) was a famous composer of his time and the conductor and teacher of the flute to King Frederic II of Prussia; the flute concerts with the king in his castle Sansscoucci in Potsdam near Berlin were reknown: *"Man wird sagen, daß der Puls des Morgens vor der Mahlzeit langsamer, als Nachmittags nach der Mahlzeit, und des Nachts noch geschwinder als Nachmittags schlage: .... Man nehme den Pulsschlag, wie er nach der Mittagsmahlzeit bis abends, und zwar wie er bey einem lustigen und aufgeräumten ... Menschen ... geht, zum Grunde: so wird man den rechten [Takt] getroffen haben."* ("What I found to be an appropriate time-giver for the tempo...is the pulse at the hand of a healthy man .... One should take the pulse of a merry and good tempered man...as it is after lunch until evening and the tempo will be fine"(Quantz, 1752, p. 206; see Figure 17). The metronome itself was not invented until 1816 by Johann Nepomuk Mälzel (1772–1838); the idea was proposed by the composer Ludwig van Beethoven, who desired a more precise device to define the tempo of music.

In subsequent years, many reports were published on the rhythm in heart rate, both in health and disease. Wilhelm Falconer (1744–1824), a British physician at the General Hospital in Bath and member of the Royal Society of Sciences of Great Britain, wrote: "*Es ist eine bekannte Sache, daß der Puls selbst im gesunden Zustand sich bedeutend in den verschiedenen Zeiten des Tages verändert*" ("It is well known that in in good health, the pulse varies at different times of the day") (Falconer, 1797, German ed., p. 24; see Figure 18).)

In 1776, Carlo Gandini also gave very precise recommendations (Gandini, 1776) of how to measure the pulse correctly by placing the fingers on the artery (see Figure 19).

M. Bordenave, a French surgeon and Royal Professor at the Royal Academy of Sciences, described that the pulse varied between waking hours and during sleep (Bordenave, 1787; see Figure 20). Similarly, the Swiss physician Johann Georg Zimmermann (1728–1795), who later in his life became the physician of many royals (Hannover, Prussia, Russia), mentioned in his book *Von der Erfahrung in der Arzneykunst* (Zimmermann, 1793) that the number of pulses in man was dependent on the time of day, temper, age, and sex (see Figure 21). Furthermore, he noticed that the pulse rate raises during fever, and recommended that the pulse is best measured by use of the second-hand of the clock (see Figure 21).



Johann Joachim Quantzens,
Königl. Preußiſchen Kammermuſikus,
Verſuch einer Anweiſung
die
Flöte traverſiere
zu ſpielen;
mit verſchiedenen,
zur Beförderung des guten Geſchmackes
in der praktiſchen Muſik
dienlichen Anmerkungen
begleitet,
und mit Exempeln erläutert.
Nebſt XXIV. Kupfertafeln.
BERLIN,
bey Johann Friedrich Voß. 1752.

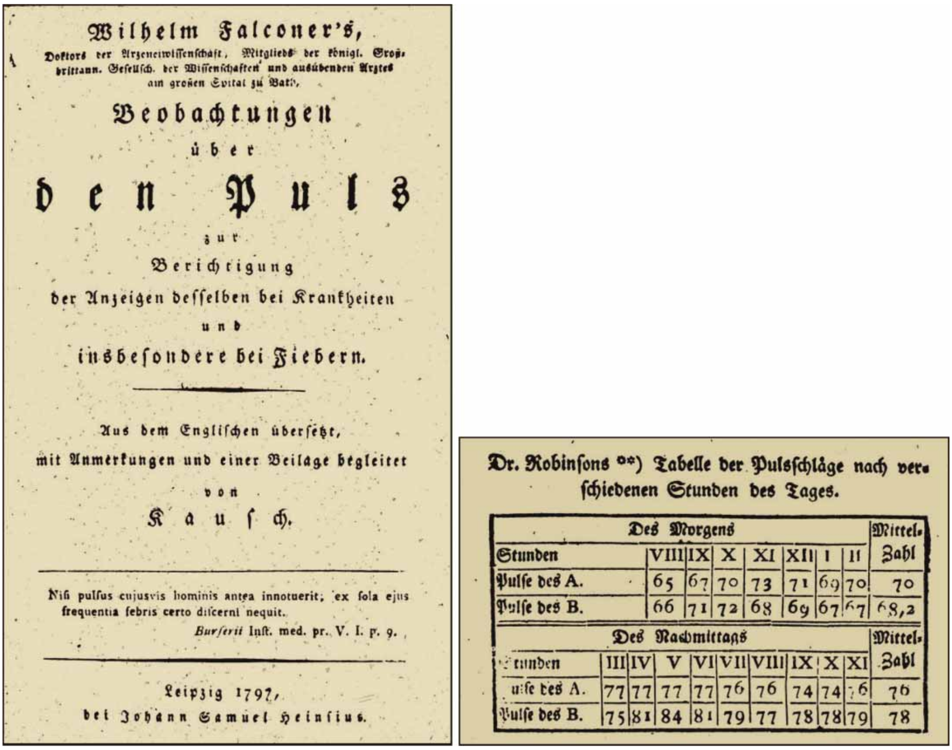
Johann Joachim Quantz
Versuch einer Anweisung die Flöte traversiere zu spielen
Neudruck
C. F. Kahnt Nachfolger Leipzig

206 Des XVII. Hauptſtücks VII. Abſchnitt.

nach zu faſſen. Man wird ſagen, daß der Puls [267] des Morgens vor der Mahlzeit langſamer, als Nachmittags nach der Mahlzeit, und des Nachts noch geſchwinder als Nachmittags ſchlage: auch daß er bey einem zur Traurigkeit geneigten Menſchen langſamer, als bey einem heftigen und luſtigen, gehe. Es kann ſeyn daß dieſes ſeine Richtigkeit hat. Dem ungeachtet aber könnte man auch dießfalls etwas gewiſſes beſtimmen. Man nehme den Pulsſchlag, wie er nach der Mittagsmahlzeit bis Abends, und zwar wie er bey einem luſtigen und aufgeräumten, doch dabey etwas hitzigen und flüchtigen Menſchen, oder, wenn es ſo zu reden erlaubet iſt, bey einem Menſchen von choleriſch-ſanguiniſchem Temperamente geht, zum Grunde: ſo wird man den rechten getroffen haben. Ein niedergeſchlagener, oder trauriger, oder kaltſinniger und

FIGURE 17 From Johann Joachim Quantz's, *Versuch einer Anweisung die Flöte traversière zu spielen*, first published in 1752; shown on the right is also a reprint of the original in 1906 (Quantz 1752, 1906).

Obviously, the day-night difference in pulse rate was one of the most prominent observations in medicine of those days. A professor at the University of Halle and subsequently Ordinarius at the Charité in Berlin, Johann Christian Reil (1759–1813)—who was also a physician to J.W. von Goethe—mentioned, "The pulse goes up when evening is coming; this is not a direct effect of some stimuli but due to an increase in sensitivity from morning to night." (Reil, 1796, p. 134; see Figure 22). The rhythm in heart rate was already presented in 1801 in a textbook on physiology. Johann Heinrich Ferdinand von Autenrieth (1772–1835),



Wilhelm Falconer's,
Doktors der Arzeneiwissenschaft, Mitglieds der königl. Großbrittann. Gesellsch. der Wissenschaften und ausübenden Arztes am großen Spital zu Bath,

Beobachtungen
über
den Puls
zur
Berichtigung
der Anzeigen desselben bei Krankheiten
und
insbesondere bei Fiebern.

Aus dem Englischen übersetzt, mit Anmerkungen und einer Beilage begleitet
von
Kausch.

Nisi pulsus cujusvis hominis antea innotuerit; ex sola ejus frequentia febris certo discerni nequit.
Burserii Inst. med. pr. V. I. p. 9.

Leipzig 1797,
bei Johann Samuel Heinsius.

Dr. Robinsons **) Tabelle der Pulsschläge nach verschiedenen Stunden des Tages.

Des Morgens								Mittel-Zahl
Stunden	VIII	IX	X	XI	XII	I	II	
Pulse des A.	65	67	70	73	71	69	70	70
Pulse des B.	66	71	72	68	69	67	67	68,2

Des Nachmittags										Mittel-Zahl
Stunden	III	IV	V	VI	VII	VIII	IX	X	XI	
Pulse des A.	77	77	77	77	76	76	74	74	76	76
Pulse des B.	75	81	84	81	79	77	78	78	79	78

FIGURE 18 Falconer's *Beobachtungen über den Puls*, with a table showing pulse rate data of two persons (A, B) in the morning and afternoon. First German edition, J S Heinsius, Leipzig, pp. 27–28 (Falconer, 1797).

a teacher of anatomy, physiology, and pharmacology at the University of Tübingen, Germany, presented exact data on the pulse rate in relation to time of day (Autenrieth, 1801, p. 209): "*Nun aber geschehen in einer Minute bey einem erwachsenen Menschen des Morgens 65–70, des Abends 75–80 Pulsschläge*" ("In an adult the pulse is about 65–70 in the morning, in the evening 75–80 beats per minute") (see Figure 23). Moreover, Virey wrote in his thesis that the heart rate is lowest 2–3 h after midnight: "*vers deux á trois heures après minuit, le pouls se relève considérablement*" (Virey, 1814, p. 28).

Interestingly, Gottlieb Tobias Wilhelm (1758–1811), a protestant clergyman and member of the Association of Doctors and Natural Scientists of Berlin and Halle, wrote in his book *Unterhaltungen über den Menschen* that pulse rate is also dependent on the frequency of breathing, differing between inhalation and exhalation (Wilhelm, 1806a; see Figure 24). Furthermore, daily variations in vasodilatation were reported by Paul-Joseph Barthez (1806). Barthez (1734–1806), a physician and French encyplopedist who was a professor at the University of Montpellier (France), became the physician to the French King (Médecin Consultant du Roi), and in 1801 he was named the physician of the First Counsul

GLI ELEMENTI
DELL'
ARTE SFIGMICA,
O SIA
LA DOTTRINA DEL POLSO
RICAVATA DALL' ANTICA, E MODERNA STORIA
DELLA MEDICINA CHINESE, ED EUROPEA,
INDI COMBINATA, E RIDOTTA A REGOLE
NON MENO SICURE, CHE FACILI
DAL DOTTOR
CARLO GANDINI,
E DEDICATA
AL MERITO IMPAREGGIABILE
DELL' ILLUSTRISSIMO SIGNORE
D. ANTONIO VILLARI
FILOSOFO, PROFESSORE DI MEDICINA ec.
IN NAPOLI MDCCLXXVI.
NELLA STAMPERIA, ED A SPESE DI GAETANO CASTELLANO.
CON LICENZA DE' SUPERIORI.

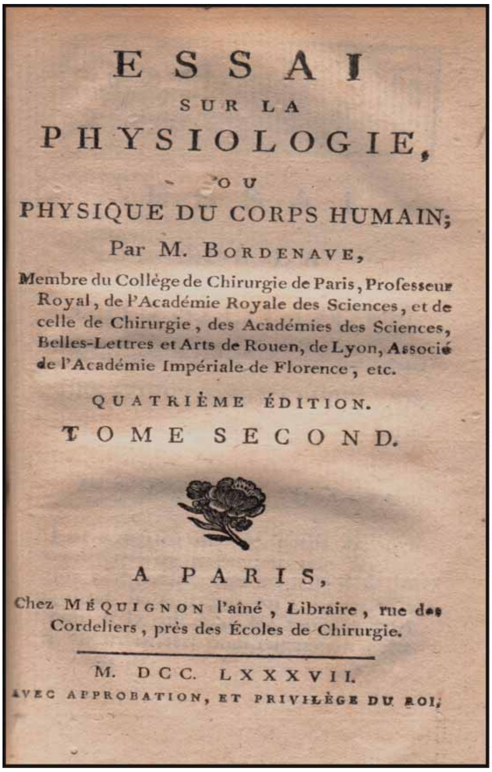
FIGURE 19 Gandini's *Gli Elementi dell' Arte Sfigmica*... G. Castello, Napoli (Gandini, 1776).

(Médecin du Premier Consul). In is book *Nouveaux Éléments de la Science de L'Homme*, he mentioned more pronounced dilation of the small vessels a night: "*La pléthora relative que je dis que le sommeil produit dans les derniers vaisseaux, est sans dout plus considerable dans les veines que dans les artères*"("The relative dilatation which I mentioned to occur during sleep in the small vessels is more pronounced in the veins than in the arteries") (Barthez, 1806, p. 241; see Figure 25).

Impact on Modern Medicine

- Development of devices for the continous monitoring of heart rate (e.g., Holter-ECG)
- Inclusion of heart rate frequency spectrum in diagnostic procedures
- Nightly dilatation of blood vessels documented

For further discussions of rhythms in heart rate, please see Lemmer (2006), Lemmer and Portaluppi (1997), and Portaluppi and Hermida (2007).


ESSAI
SUR LA
PHYSIOLOGIE,
OU
PHYSIQUE DU CORPS HUMAIN;
Par M. BORDENAVE,
Membre du Collège de Chirurgie de Paris, Professeur Royal, de l'Académie Royale des Sciences, et de celle de Chirurgie, des Académies des Sciences, Belles-Lettres et Arts de Rouen, de Lyon, Associé de l'Académie Impériale de Florence, etc.
QUATRIÈME ÉDITION.
TOME SECOND.
A PARIS,
Chez MÉQUIGNON l'aîné, Libraire, rue des Cordeliers, près des Écoles de Chirurgie.
M. DCC. LXXXVII.
AVEC APPROBATION, ET PRIVILÈGE DU ROI.

Le pouls varie par différantes circonstances, ... selon la veille ou le sommeil, selon le tempérament, selon le sexe; ...
il est plus fréquant le soir que le matin á raison de la vielle, et peut-être est-ce la cause naturelle du paroxisme qui arrive le soir dans presque toutes les fièvres.

FIGURE 20 Bordenave's *Essai sur la Physiologie*, describing variations in pulse during wakeness and sleep (Bordenave, 1787).

RHYTHM IN BLOOD PRESSURE

The English physiologist, chemist, and inventor Stephan Hales (1677–1761) was the first to directly study blood pressure in living animals (Hales, 1733, 1748c, 1780). Hales is best known for his *Statical Essays*. The first volume, *Vegetable Staticks* (Hales, 1727, 1748a, 1779), contains an account of numerous plant physiology experiments (i.e., water loss from plants by evaporation, rate of growth of shoots and leaves, variations in root-force at different times of the day, etc.). The second volume (Hales, 1733, 1748b, 1748c, 1780) of *Haemostaticks*, containing experiments on the "force of the blood," its rate of flow, capacity of the different vessels, etc., in various animals qualifies him to be regarded as one of the originators of experimental physiology (see Figure 26). His book provided the first quantitative estimates of blood pressure. A glass tube inserted directly into the carotid artery of a horse permitted him to directly measure arterial pressure (i.e., as the height attained by the level of the column of blood). Hales was actually the inventor of the sphygmomanometer. This epochal work, so important to therapeutics ever

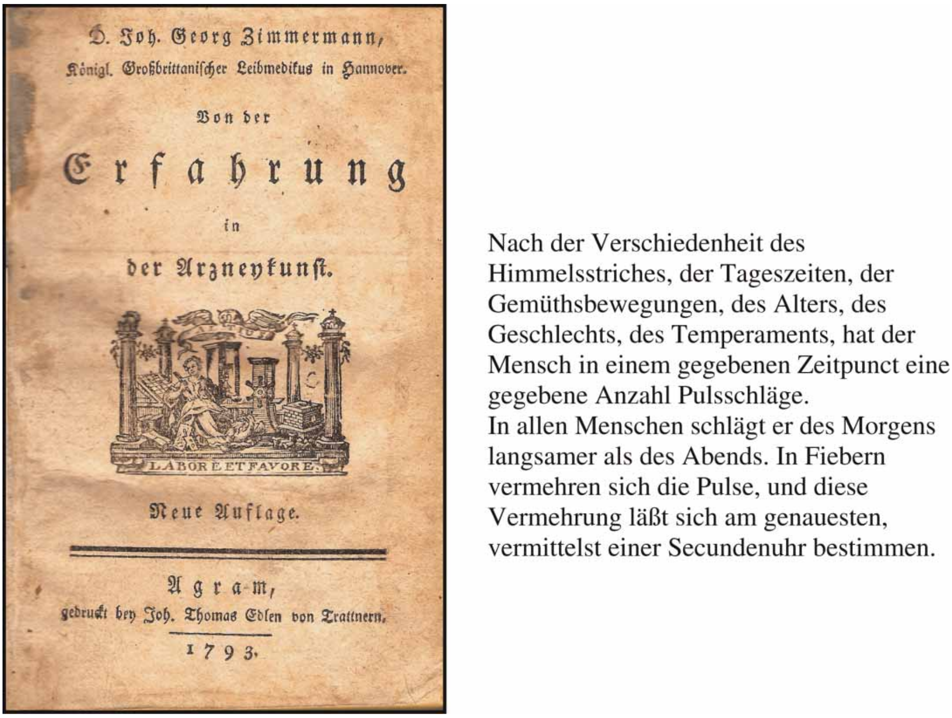
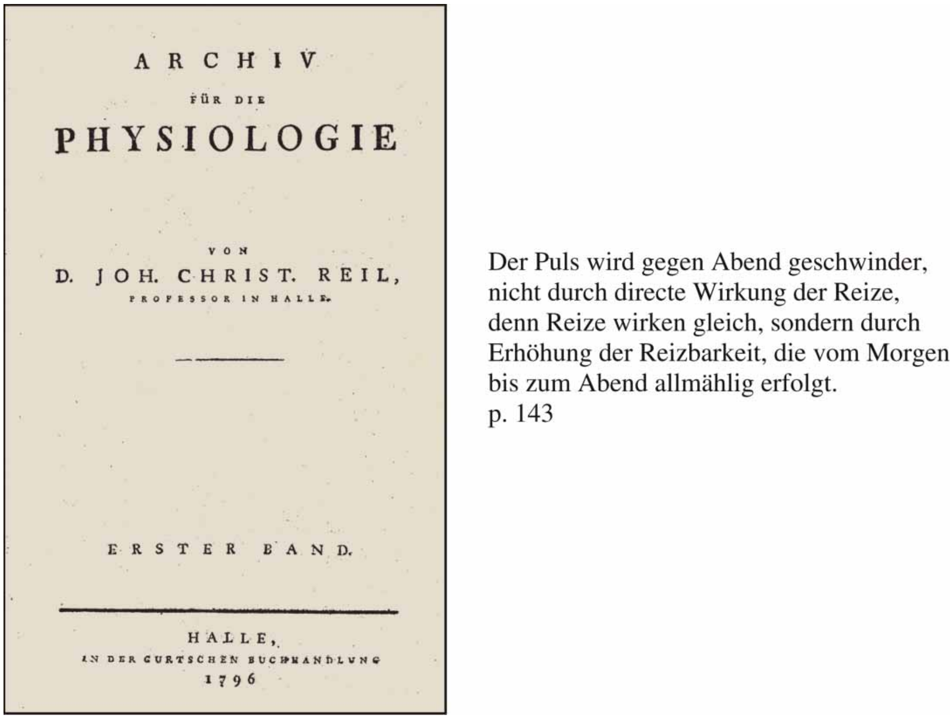


FIGURE 21 Cover page of Zimmermann's book, *Von der Erfahrung der Arzneykunst*, von J.T. Edlen von Trattnern, Agram (Zimmermann, 1793).

since, was the most important step in the knowledge of circulation between Malpighi and Poiseuille.

With the advent of plethysmographic devices (e.g., Riva-Rocci, 1896; von Basch, 1881; Zadek, 1881), it was also observed that blood pressure in healthy and diseased persons may not be constant throughout 24 h (see Figure 27). However, it was Zadek (1881) who first presented detailed data on daily variations (*Tagesschwankungen*) in blood pressure, with an increase in the afternoon and a drop at night. Even different types of hypertension were described at the beginning of the 20th century based on their different 24 h blood pressure profiles (Katsch & Pansdorf, 1922; Müller, 1921a, 1921b).

The English physician, James Hope (1801–1841), a member of the Royal Society of the Sciences in London, reported in his book *Von den Krankheiten des Herzens und der großsen Gefäßse* many situations in detail in which the rhythm of heart rate was modified by various diseases (Hope, 1833; see Figure 28). In addition, he described the symptoms of angina pectoris quite clearly: "*… so beginnt sie mit einem Gefühle von Schmerz und Zusammenschnürung in der Präcordialgegend, verbunden mit einer mehr oder minder schmerzhaften Taubheit in dem linken Arme…*."



ARCHIV
FÜR DIE
PHYSIOLOGIE

VON
D. JOH. CHRIST. REIL,
PROFESSOR IN HALLE.

ERSTER BAND.

HALLE,
IN DER CURTSCHEN BUCHHANDLUNG
1796

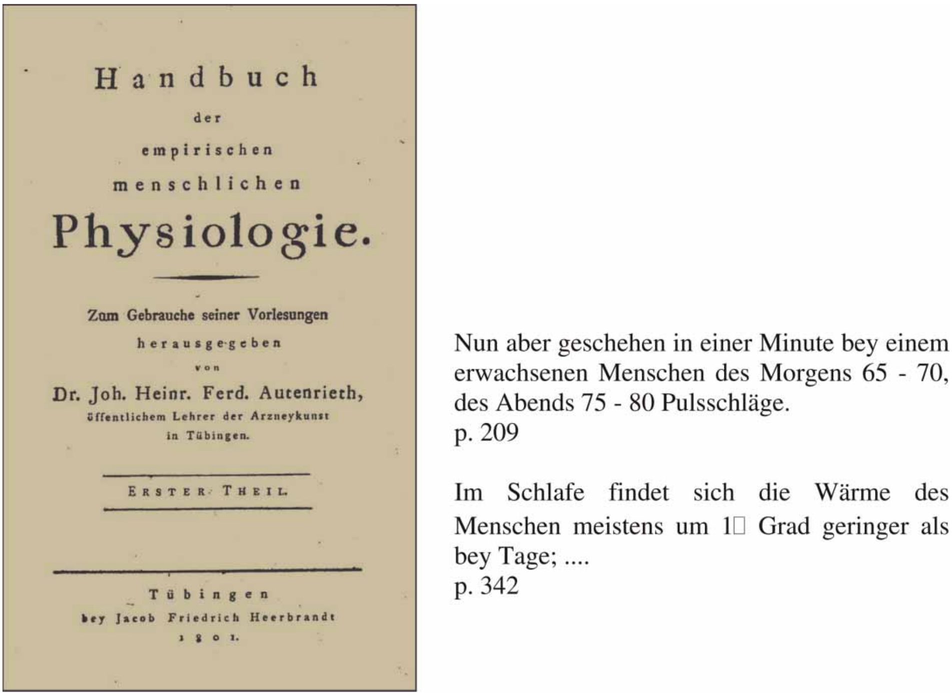
FIGURE 22 Reil's *Von der Lebenskraft*, Archiv für die Physiologie, Gurtsche Buchhandlung, Halle (Reil, 1796).

("It starts with a sensation of pain and constriction in the precordial area, in conjunction with a more or less painful deafness in the left arm") (p. 392).

Impact on Modern Medicine

- Development of ambulatory blood pressure monitoring devices (ABPM)
- 24 h blood pressure profile of diagnostic value for differentiating subtype forms of hypertension (primary, secondary hypertension), related to blood pressure values at night (dippers, non-dippers, super-dippers, risers)
- Disturbed circadian blood pressure profiles as risk factors in severe hypertension, kidney disease, endocrine diseases, diabetes mellitus, sleep aponea, etc.
- Office (white-coat) hypertension defined as a distinct (pre)form of hypertension

For further discussions of rhythms in blood pressure, please see Hermida et al. (2007), Lemmer (2006), and Middeke and Lemmer (1996).


Handbuch
der
empirischen
menschlichen
Physiologie.

Zum Gebrauche seiner Vorlesungen
herausgegeben
von
Dr. Joh. Heinr. Ferd. Autenrieth,
öffentlichem Lehrer der Arzneykunst
in Tübingen.

Erster Theil.

Tübingen
bey Jacob Friedrich Heerbrandt
1801.

Nun aber geschehen in einer Minute bey einem erwachsenen Menschen des Morgens 65 - 70, des Abends 75 - 80 Pulsschläge.
p. 209

Im Schlafe findet sich die Wärme des Menschen meistens um 1□ Grad geringer als bey Tage; ....
p. 342

FIGURE 23 Cover page of Autenrieth's *Handbuch der empirischen menschlichen Physiologie*, Part 1. Tübingen, JF Heerbrandt, 1801 (Autenrieth, 1801, pp. 209, 277, 343).

RHYTHM IN BODY TEMPERATURE, BODY WEIGHT, AND PERSPIRATION

In 1782, the German physician Christoph Friedrich Elsner (1749–1820), a professor of medicine at the University of Königsberg, Germany, published a book on the "daily lapse of fever" (see Figure 29): "The daily lapse of fever attack ... is due to a general law in nature responsible for a daily revolution in the human body such as the regular occurrence of sleep, of wakeness, of hunger, and evacuations as well as in the evening pulse. This revolution ... results in more or less variations in all kinds of fever during the day. One could name these changes the daily lapse of fever"(Elsner, 1782, p. 36).

The great physiologist Sanctorius Sanctorius (1561–1636) was a professor at Padua from 1611 to 1624 where he performed experiments, including self-experiments involving body temperature, respiration, and weight. On a daily basis for a period of 30 yrs (*"triginta annorum experimentis ad perfectionem deduxi"*), Sanctorius weighed himself (see Figure 30), everything he ate and drank, plus his urine and feces. He compared the weight of what he had eaten to that of his waste products, the latter being considerably smaller. He developed the theory of

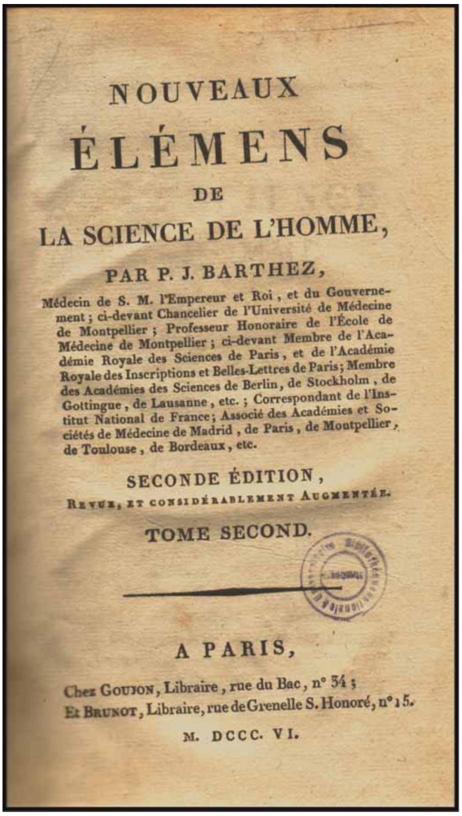
Warum beym Einathmen der Puls schneller geht...

Man kann zwischen Aus= und Einathmen vier bis fünf Pulsschläge zählen. So würden also während 60 - 70 Pulsschlägen 17 - 18 Einathmungen erfolgen.

FIGURE 24 Cover page of Wilhelm's *Unterhaltungen über den Menschen*, Martin Engelbrecht'sche Kunsthandlung, Augsburg (Wilhelm, 1806a).

insensible perspiration in an attempt to account for this difference. The "weighing chair" *("sella")*, which he constructed and employed during these experiments *("ex usus istius sella")* is famous. He calculated the water loss due to sweating ("*perspiration sensibilis*") and evaporation ("*perspiration insensibilis*") during sleep, wakening, exercise, and rest (Sanctorius 1664, 1753; see Figure 31). In his aphorisms, Sanctorius Sanctorius reported sleep increases evaporation from the skin and even gave details on the extent of the weight loss of perspiration: "… *ut septem horis quinquaginta unciae cocti perspirabilis … exhalent*" ("50 ounces in 7 hours") (Sanctorius, 1664, p. 2, 1753).

A daily rhythm in body temperature of man was reported by J. Davy in 1845 (Davy 1845). In 1868, Carl Reinhold August Wunderlich (1815–1877), a professor at the Medical Clinic Tuebingen and subsequent professor in Leipzig, reported detailed observations on the 24 h rhythm in body temperature. Interestingly, he also presented much data and numerous figures on the day-night variation in body temperature in various disease states (Wunderlich, 1868). He observed that these day-night variations in body temperature even persisted—though at a different level—during disease (e.g., typhus; see Figure 32). Barthez (1806,



NOUVEAUX
ÉLÉMENS
DE
LA SCIENCE DE L'HOMME,
PAR P. J. BARTHEZ,
Médecin de S. M. l'Empereur et Roi, et du Gouvernement; ci-devant Chancelier de l'Université de Médecine de Montpellier; Professeur Honoraire de l'École de Médecine de Montpellier; ci-devant Membre de l'Académie Royale des Sciences de Paris, et de l'Académie Royale des Inscriptions et Belles-Lettres de Paris; Membre des Académies des Sciences de Berlin, de Stockholm, de Gottingue, de Lausanne, etc.; Correspondant de l'Institut National de France; Associé des Académies et Sociétés de Médecine de Madrid, de Paris, de Montpellier, de Toulouse, de Bordeaux, etc.
SECONDE ÉDITION,
REVUE, ET CONSIDÉRABLEMENT AUGMENTÉE.
TOME SECOND.
A PARIS,
Chez GOUJON, Libraire, rue du Bac, n° 34;
Et BRUNOT, Libraire, rue de Grenelle S. Honoré, n° 15.
M. DCCC. VI.

FIGURE 25 Barthez's *Nouveaux Éléments de la Science de L'Homme*. Second Édition, Paris, Goujon et Brunot (Barthez, 1806).

p. 147) also reported on the day-night variation in body temperature: "*Dans le sommeil … la chaleur de l'habitude du corps est moindre que dans la veille*" ("During sleep the body temperature … is less than during wakening") (see Figure 25).

ANGINA PECTORIS

The British physician William Heberden is credited with the first description of angina pectoris: "There is a disorder of the breast, marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare, of which I do not recollect any mention among medical authors. The seat of it, and sense of strangling and anxiety with which it is attended, may make it not improperly be called angina pectoris"(Heberden, 1772). A couple of decades later, in 1793, the Swiss physician Zimmermann (1728–1795) mentioned in his book *On our Knowledge in Medicine* (see Figure 21) that the symptoms of angina pectoris

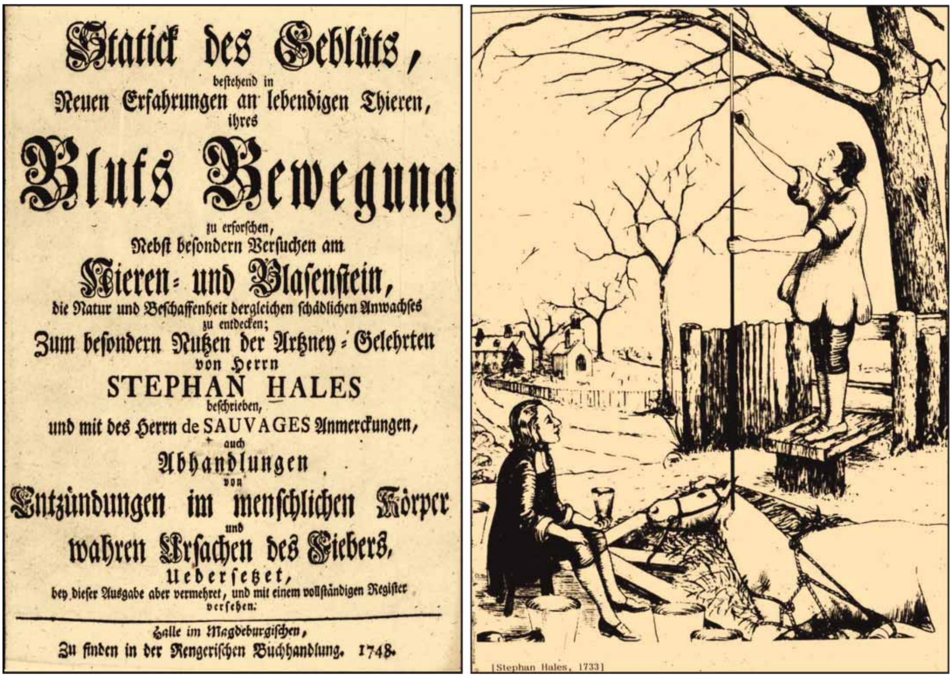

Statick des Geblüts,
bestehend in
Neuen Erfahrungen an lebendigen Thieren,
ihres
Bluts Bewegung
zu erforschen,
Nebst besondern Versuchen am
Nieren- und Blasenstein,
die Natur und Beschaffenheit dergleichen schädlichen Anwachses
zu entdecken;
Zum besondern Nutzen der Artzney-Gelehrten
von Herrn
STEPHAN HALES
beschrieben,
und mit des Herrn de SAUVAGES Anmerckungen,
auch
Abhandlungen
von
Entzündungen im menschlichen Körper
und
wahren Ursachen des Fiebers,
Uebersetzet,
bey dieser Ausgabe aber vermehret, und mit einem vollständigen Register
versehen.
Halle im Magdeburgischen,
Zu finden in der Rengerischen Buchhandlung. 1748.

FIGURE 26 Stephan Hales' famous book, *Haemostaticks*, the German edition form 1748. (Hales, 1748b) Right: A contemparatory picture showing Hale's experiment of determining the blood pressure in a living horse.

("*Engbrüstigkeit*") persist during the nighttime hours: "…wie in der Engbrüstigkeit, die … wenigstens bey der Nacht immer gleich ist" (Zimmermann, 1793).

Friedrich Casimir Medicus (1736–1808), a physician in Mannheim, Germany, published a wonderful book *Geschichte periodischer Krankheiten* (see Figure 33), in which he presented many examples of the periodic occurrence of disease onset (Medicus, 1764, p. 43). In Figure 33, the morning onset of angina pectoris is described in a patient.

In 1810, the German botanist and physician Kurt Sprengel (1766–1833) was the first to publish in his *Handbuch der Pathologie* that a certain kind of angina pectoris, so-called *Brustbräune*, has a typical nocturnal onset: "…during night, after the first calm sleep, the first attack is observed during night and consequent attacks occur in the morning" (Sprengel, 1810, pp. 135, 136, 230, 231; see Figure 34).

An Italian professor of medicine at the University of Bologna, Antonio Guiseppe Testa (1756–1814), described in 1815 the symptoms of angina attacks that occur during the nighttime hours: "… *drückender Schmerz, Anfälle von Ohnmachten und Erstickungsgefahr … vor allem zur Nachtzeit*" ("…deep pain, episodes of fainting and danger of asphyxia… mainly during the night)." He also stated in his text that recent observations of

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MÜNCHENER MEDIZINISCHE WOCHENSCHRIFT.

ORGAN FÜR AMTLICHE UND PRAKTISCHE ÄRZTE.

Zusendungen sind zu richten für die Schriftleitung: Arnulfstr. 26 (Sprechstunden 8½–1 Uhr für Bezug: an J. F. Lehmanns Verlag, Paul Heyse-Strasse 2 für Anzeigen: L. Waibel, Anzeigen-Verwaltung, Theatinerstr.

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Originalien.

Aus der Medizinischen Universitätsklinik Frankfurt a. M. (Direktor: Prof. G. v. Bergmann.)

Die Schlafbewegung des Blutdrucks.

Von G. Katsch und H. Pansdorf.

Wir haben gelernt, den Blutdruck bei Hypertonikern nicht als feste Niveaulage anzusehen, die nach einmaliger Messung mehr oder weniger endgültig bekannt ist: das Interesse wächst für die Blutdruckbewegungen. So hat man schon länger labile und transitorische Formen der Hypertonie kennen gelernt; neben Pal, Ambard, Kylin, Schürer und Moog hat besonders Fahrenkamp sehr instruktive Kurven gewonnen, in denen er bei Hypertonikern eine Zeitlang mehrmals täglich Maximaldruck und Minimaldruck bestimmte. Untersuchungen von F. Kaufmann an unserer Klinik bestätigten die Fahrenkampschen Befunde. Es leuchtet ein, dass durch eine Beschäftigung mit den Blutdruckbewegungen Rückschlüsse möglich werden können auf die bewegenden Kräfte. So dass wir etwas gewinnen für die noch so dunkle Dynamik der Hypertensionen.

Die grösste physiologische Blutdruckbewegung ist das Absinken des Blutdrucks im Schlaf. So altbekannt diese Tatsache ist, so extrem spärlich sind Ansätze, die Beobachtung dieser grössten Schwankung des arteriellen Druckes klinisch auszumünzen. Im vorigen Jahr ist, soweit wir sehen, der erste Versuch gemacht, „die Messung des Blutdrucks am Schlafenden als klinische Methode" einzuführen (Carl Müller aus der Nicolay-

druck und Minimum (vergl. Abb. 1). Dem Kranken Schlafmittel zu geben, is bei dieser Technik nicht erforderlich. Die einzige Störung, die in Einzelfälle vorkam, bestand darin, dass die Schläuche durch Bewegungen des schlafende Kranken am Rand der Bettdecke abgeknickt wurden.

Beobachtungen.

Die Registrierung der nächtlichen Blutdruckkurve, die wir in de geschilderten Weise bei zahlreichen Kranken ausführten, hat mancherlei interessante Befunde geliefert. Mühelos machen wir von neuen die bekannte Feststellung: dass der maximale Druck an stärksten während der ersten zwei Schlafstunden sinkt und sich von dem dann erreichten Tiefpunkt ganz allmählich bis zum morgendlichen Erwachen wiedererhebt. (Vergl. Fig. 2a und Fig. 7b.) Beim Erwachen selbst wird mehr oder weniger diskontinuierlich auf den Tagwert hinaufreguliert. (Vergl. Fig. 2—7 die ausgezogene Linie Ma). Die nicht seltene Apoplexie beim Erwachen wird uns durch dieses plötzliche Hinaufregulieren verständlicher.

Individuelle Abweichungen von diesen typischen Kurven kommen vor. Wir fühlen uns in vielen Fällen berechtigt, die individuelle Druckkurve während des Nachtschlafes zu betrachten als eine Art Schlaftiefenkurve. So findet sich z. B. in Fig. 2b der tiefste Punkt des Maximaldruckes morgens unmittelbar vor dem Wecken, mit dem viele unserer Versuche beendet wurden. In der Regel ist der Tiefpunkt zwischen 12 oder 1 Uhr. Der Zeitpunkt des Einschlafens ist natürlich von Einfluss. Gaupp hat als solche Schlaftiefenkurven mit psychologischer Methodik Kurven der Weckbarkeit ermittelt und auf die Wichtigkeit der Schlaftiefenkurven für das Verständnis der Schlafstörungen hingewiesen (Morgenschläfer, Abendschläfer). Wir sehen keinen Nachteil darin, dass

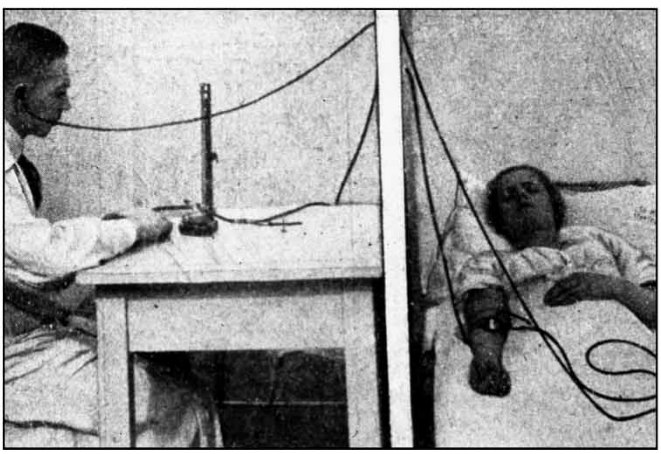
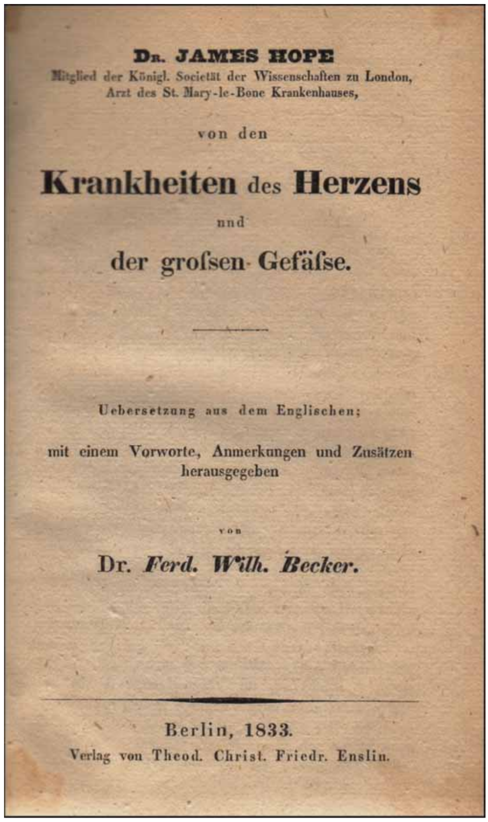


FIGURE 27 Blood pressure monitoring during sleep at night by use of a long stethoscope (Katsch & Pansdorf, 1922).

physicians clearly show angina attacks occur in the early morning hours: "Kapitel XII *Von den Kennzeichen der Brustbräune: Auch die frühen Morgenstunden sind dazu sehr geeignet*" (Testa, 1815; see Figure 35). It is important to note that early in the 19th century, it was not possible to differentiate between stable angina pectoris (pain and ST-segment depression in the ECG during the daytime) and vasospastic Prinzmetal angina (symptoms of pain and ECG abnormalities at night) (see Lemmer, 2006, 2007b).



Dr. JAMES HOPE
Mitglied der Königl. Societät der Wissenschaften zu London,
Arzt des St. Mary-le-Bone Krankenhauses,

von den

Krankheiten des Herzens

und

der grofsen Gefäfse.

Uebersetzung aus dem Englischen;

mit einem Vorworte, Anmerkungen und Zusätzen
herausgegeben

von

Dr. *Ferd. Wilh. Becker.*

Berlin, 1833.
Verlag von Theod. Christ. Friedr. Enslin.

FIGURE 28 James Hope's *Von den Krankheiten des Herzens und der grossen Gefässe*. German edition, Berlin, Verlag Theodor Christian Friedrich Enslin (Hope, 1833).

Impact on Modern Medicine

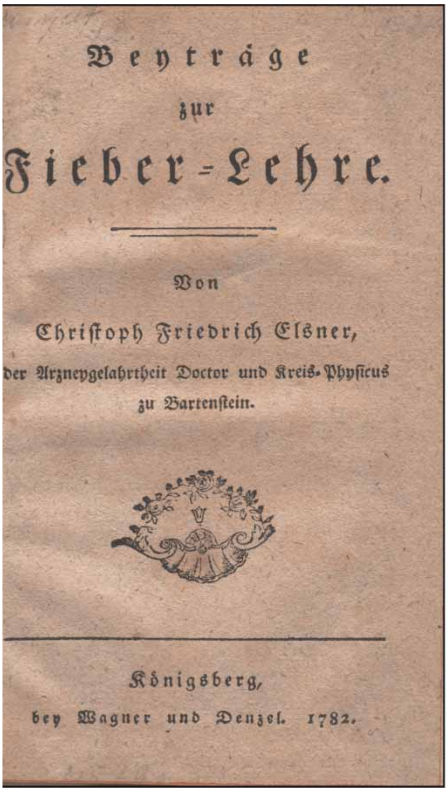
- Circadian profiles of cardiovascular events (myocardial infarction, sudden cardic death, stroke, angina pectoris) well established
- Diurnal variation in drug effectiveness in various types of angina

For further discussions of angina pectoris, please see Gallerani et al. (2007), Lee et al. (2008), Leibowitz et al. (2007), Lemmer (2006), Portaluppi and Lemmer (2007), and Smolensky et al. (2007a).

PSYCHIATRIC DISORDERS

In 1764, Medicus first described the symptom of winter depression: "Each year Dr. Helwig noticed during the month of December that depression reappeared in a patient" (see Figure 36).

Sleep disturbancies in melancholia, however, had been earlier described by Geiger (1606–1671), a personal physician to the Bavarian


Beyträge
zur
Fieber-Lehre.
Von
Christoph Friedrich Elsner,
der Arzneygelahrtheit Doctor und Kreis-Physicus
zu Bartenstein.
Königsberg,
bey Wagner und Denzel. 1782.

Den Verlauf eines Fieber Anfals ... aus de allgemeinen Naturgesetz, welches macht, daß alle Tage eine gewisse Revolution in dem menschlichen Körper vorgeht, wie solches aus der regelmäßigen Wiederkehr des Schlafes, des Wachens, der Eßlust, der Ausleerungen und Veränderungen des Pulses am Abende, erhellet. Diese Revolution macht, daß in allen Fiebern, selbst in den sogenannten anhaltenden, täglich eine gewisse mehr oder weniger merkliche Remission und Exacerbation bemerkt wird. Man erlaube mir diese Veränderung den täglichen Ablauf des Fiebers zu nennen.

FIGURE 29 Elsner's *Beyträge zur Fieber=Lehre*, Wagner und Denzel, Königsberg (Elsner, 1782).

Elector Maximilian in Munich: "On the signs of hypochondric mood both in diagnostics and pathognomonics: First of all being awake after midnight is not pleasant . . . Even if the patient sleeps well from supper to midnight there is a threat to be awake for hours . . . Others might not sleep sufficiently at all"(Geiger, 1652, p. 82; see Figure 37). In a similar manner, sleep disturbances in depression (melancholy) were described by Sprengel (see Figure 36). Sprengel also described that depression (*melancholia*) has a typical daily pattern, with "*Der Melancholiker schläft nie ganz ruhig: er fährt sehr oft aus dem Schlafe auf: . . . und fühlt sich des Morgens mehrentheils müder als am Abend*" ("increased tiredness in the morning hours than in the evening." (Sprengel, 1810, p. 309; see Figure 38).

In 1946, Helmut Marx (1901–1945), a physician at the Universities of Heidelberg and Berlin, first described the effects of lack of light on physiological functions in soldiers living at the polar circle, an observation that is now recognized as a characteristic cause of winter depression: "The changes observed cannot be explained by a lack of light. The changes in the rhythm of light exposure might be of greater importance"(Marx, 1946; see Figure 39).

FIGURE 30 The weighing chair (*sella sedento*) of Sanctorius Sanctorius shown in his book, *De Statica Medicina*, with which he determined the perspiration insensibilis and performed around-the-clock experiments on himself for 30 yrs (Sanctorius, 1664).

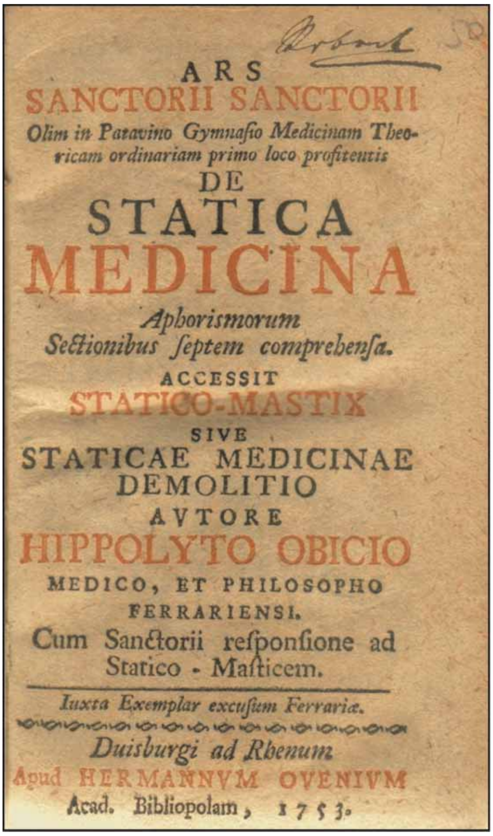
Impact on Modern Medicine

- Sleep disturbances regarded as (early) signs of depression
- Daily rhythm of symptoms in depression accepted
- Definition of winter depression included in the Diagnostic Statistic Manual of Psychiatric Diseases (DSM IV)
- Therapeutic value of (early morning) bright light in winter depression

For further discussions of psychiatric disorders, please see Lewy et al. (2006) and Wirz-Justice (2008).

METABOLIC DISORDERS

Many early reports address the 24 h variation in the symptoms of gout. In 1697, Sydenham (1624–1689) described the symptoms of gout as being more severe in the evening with easing during the early morning hours (see Figure 40): "*A Treatise of the Gout and Dropsie. There are thousand fruitful*



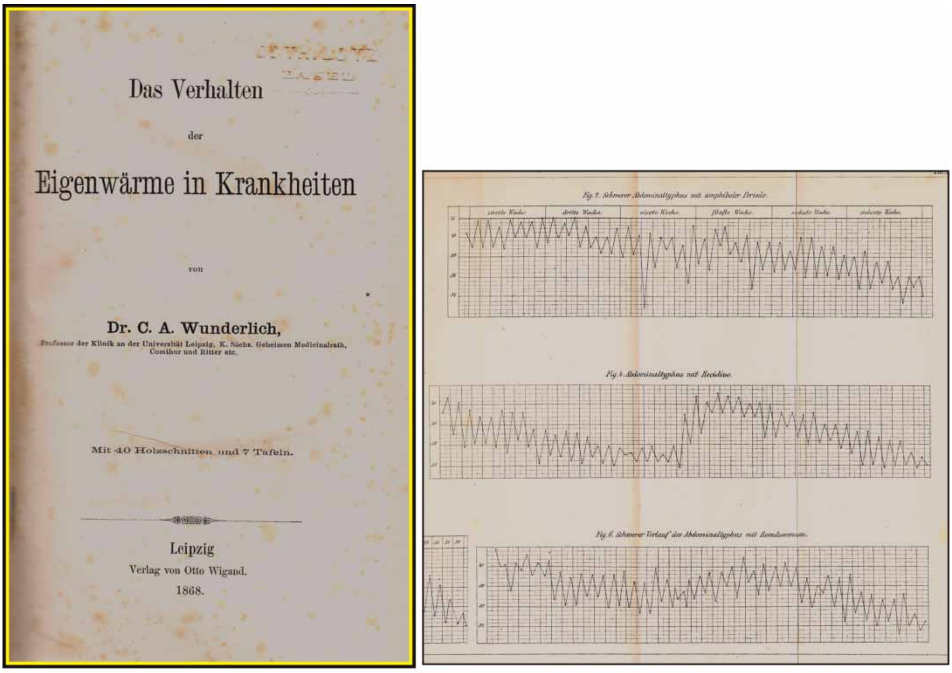
Somnus placidus adeo favet perspiratio, ut septem horis quinquaginta unicae cocti perspirabilis ... exhalent.

p. 60

FIGURE 31 Sanctorius Sanctorius' *De Statica Medicina Aphorismorum*, in which he calcuated the water loss due to perspiration during sleep (Sanctorius, 1753).

endeavours to ease the pain, . . . yet there is no ease to be had, till two or three a Clock in the Morning at which time the Sick has suddenly ease . . . ; . . . yet the pain always returns in the Evening, and is not so great in the morning . . ." (Sydenham, 1697, p. 215). He also differentiated between rheumatism and gout (Sydenham, 1697). Similar observations were reported by Caelius Aurelianus when he described that the joints are affected by arthritis and the feet by gout (*podagra*): "*. . . altera cummuniter ab articulis omnibus, altera specialiter a pedus. . . . Nam podagra pedum tantummodo doler est. Arthritis vero etiam cunctorum articulorum, sive multorum*"(Aurelianus, 1722, p. 557).

Other accounts of gout were published later. Coste (1768) described gout as a disease of the rich people and that the symptoms peak in the evening (see Figure 41). Sprengel also described the 24 h variation in the symptoms of gout in 1810 (Sprengel, 1810, p. 125) and mentioned the pain in the peripheral joints of the feet and toes mainly occurs in the night (see Figure 42). Finally, the nocturnal occurrence of gout was mentioned by Murat in his book (Murat, 1806).



Die Eigenwärme, wie sie schon im Normalzustande Schwankungen im Laufe von 24 Stunden zeigt, lässt solche auch in Krankheiten bemerken.
Bei der Verwerthung eines Messungsresultates ist die Tageszeit, in welcher die Beobachtung gemacht wird, wohl in Betracht zu ziehen.
pp. 13, 199

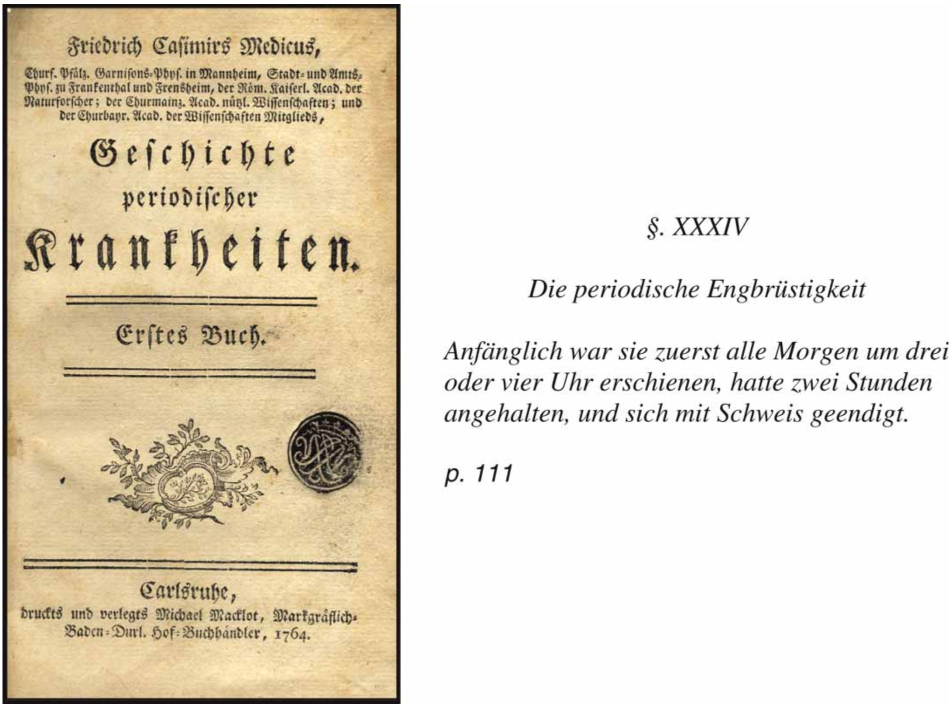
FIGURE 32 Wunderlich's *Verhalten der Eigenwärme in Krankheiten*, O. Wigand, Leipzig (Wunderlich, 1868).

As previously mentioned, Sydenham also described the symptoms of rheumatism in detail (Sydenham, 1697, p. 453) in *Chapter V—of a Rheumatism: "... It begins with shivering and shaking, and presently heat, restlesness, and thirst; and other symptoms follow which accompany a Fever. ... The patient is troubled with a violent Pain, soemtimes in this, sometimes in that Joint, in the Wrists and Shoulders, but most commonly in the knee."*

In addition, Sprengel in 1807 described a time-of-day dependency in the symptoms of rheumatic fever (see Figure 43), with main symptoms occurring most prominently in the evening (Sprengel, 1807); however, he did not mention whether the symptoms of rheumatoid arthritis vary with time of day.

Impact on Modern Medicine

- Morning pain and stiffness of joints are considered pathognomonic for Rheumatoid Arthritis


Friedrich Casimirs Medicus,
Churf. Pfälz. Garnisons-Phys. in Mannheim, Stadt- und Amts-Phys. zu Frankenthal und Frensheim, der Röm. Kaiserl. Acad. der Naturforscher; der Churmainz. Acad. nützl. Wissenschaften; und der Churbayr. Acad. der Wissenschaften Mitglieds,

Geschichte periodischer Krankheiten.

Erstes Buch.

Carlsruhe, druckts und verlegts Michael Macklot, Markgräflich-Baden-Durl. Hof-Buchhändler, 1764.

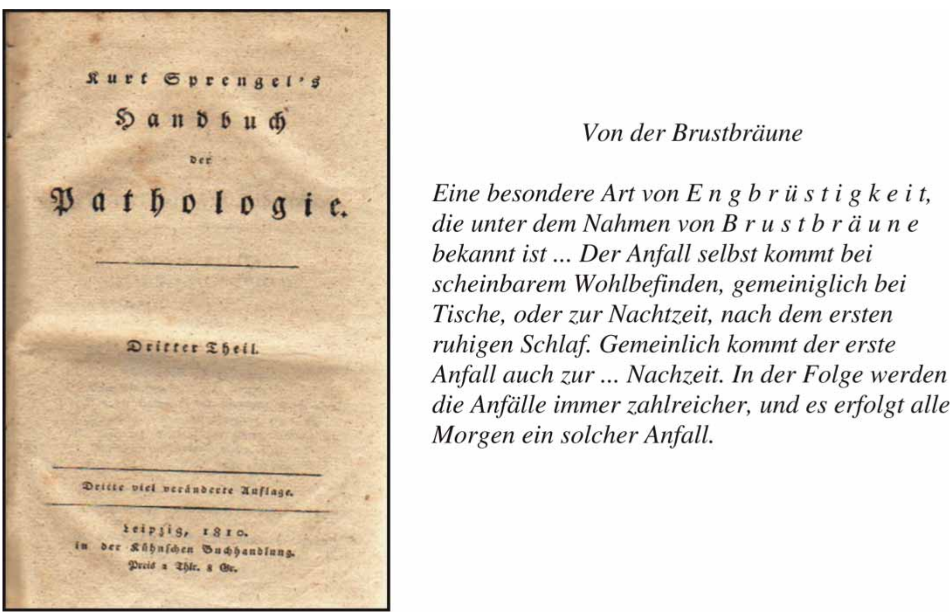
§. XXXIV

Die periodische Engbrüstigkeit

Anfänglich war sie zuerst alle Morgen um drei oder vier Uhr erschienen, hatte zwei Stunden angehalten, und sich mit Schweis geendigt.

p. 111

FIGURE 33 Medicus's *Geschichte periodischer Krankheiten*, first book, M. Macklot, Carlsruhe (Medicus, 1764).


Kurt Sprengel's
Handbuch
der
Pathologie.

Dritter Theil.

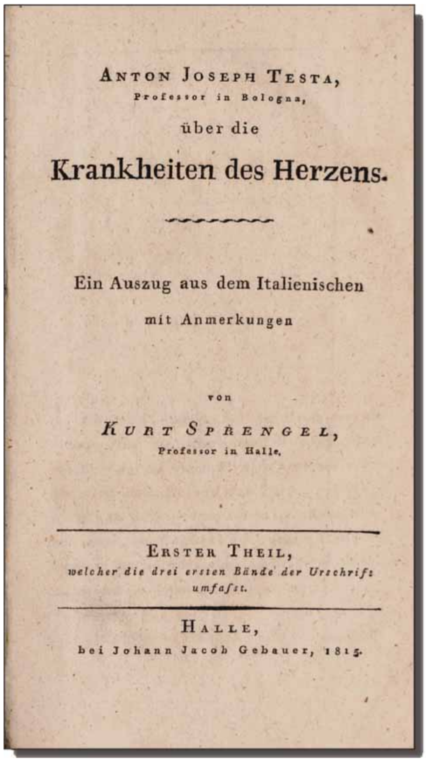
Dritte viel veränderte Auflage.

Leipzig, 1810.
in der Kühnschen Buchhandlung.
Preis 2 Thlr. 8 Gr.

Von der Brustbräune

Eine besondere Art von E n g b r ü s t i g k e i t, die unter dem Nahmen von B r u s t b r ä u n e bekannt ist ... Der Anfall selbst kommt bei scheinbarem Wohlbefinden, gemeiniglich bei Tische, oder zur Nachtzeit, nach dem ersten ruhigen Schlaf. Gemeinlich kommt der erste Anfall auch zur ... Nachzeit. In der Folge werden die Anfälle immer zahlreicher, und es erfolgt alle Morgen ein solcher Anfall.

FIGURE 34 Sprengel's *Handbuch der Pathologie*. Leipzig, Kühnsche Buchhandlung, p. 135/230 (Sprengel, 1810, pp. 135, 136, 230, 231).



ANTON JOSEPH TESTA,
Professor in Bologna,
über die
Krankheiten des Herzens.

Ein Auszug aus dem Italienischen
mit Anmerkungen
von
KURT SPRENGEL,
Professor in Halle.

ERSTER THEIL,
welcher die drei ersten Bände der Urschrift umfaſst.

HALLE,
bei Johann Jacob Gebauer, 1815.

XII.
Von den Kennzeichen der Verknöcherungen und der sogenannten Brustbräune.

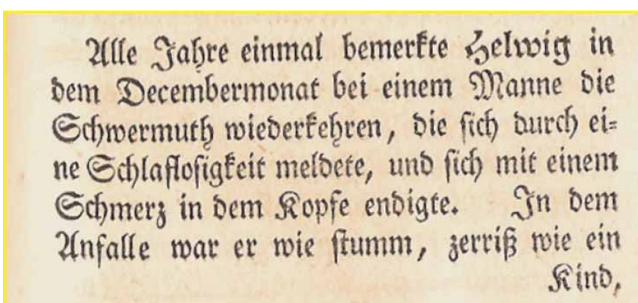
Zu den Krankheiten, welche die Untersuchungen neuerer Aerzte in ein helleres Licht gesetzt haben, wenn sie gleich selbst nicht neu sind, gehört die sogenannte Brustbräune.......

Doch haben Veränderungen in der Atmosphäre, besonders zu großse Hitze und Kälte, ferner die Annäherung der Nacht und die Stunden der Verdauung einigen Einflußs auf die Erregung der Zufälle. Auch die ersten Frühstunden sind dazu sehr geeignet.

FIGURE 35 First and only edition in German of Testa's book, *Delle Malattie del Cuore, Loro Cagioni, Specie, Segni e Cura* (Testa, 1815).

- Circadian rhythms in cytokines established in rheumatoid arthritis
- Evening dosing of non-steroidal antirheumatic drugs recommended
- Recognition gout attacks occur at night

For further discussions of metabolic disorders, please see Labrecque et al. (1995) and Straub and Cutolo (2007).



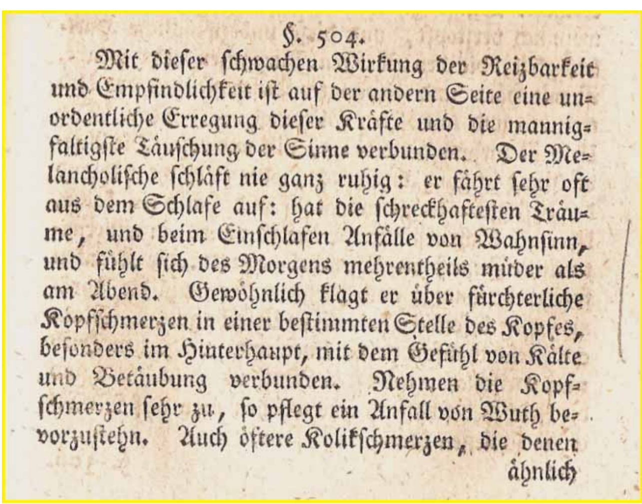
Alle Jahre einmal bemerkte Helwig in dem Decembermonat bei einem Manne die Schwermuth wiederkehren, die sich durch ei= ne Schlaflosigkeit meldete, und sich mit einem Schmerz in dem Kopfe endigte. In dem Anfalle war er wie stumm, zerriß wie ein Kind,

FIGURE 36 Observation of winter depression by Medicus in *Geschichte periodischer Krankheiten*, M. Macklot, Carlsruhe (Medicus, 1764).

De signis tam Diagnosticis quam Pathognomonicis Affectionis hypochondria

In primis vero vigiliae post mediam noctem, pleroque molestare solent. Etsi enim post coenam, ad mediam nocte satis bene dormiunt: Tamen postea vigilant, manent vigiles per aloquot horas ... : alli vero non amplius dormire possunt.

FIGURE 37 Front page of Malachias Geiger's book on depression, *Microcosmus Hypochondriacus Sive de Melancholia* . . . (Geiger, 1652). Below the title cylinder, the melancholic patient is lying in his bed; to his right the physician is presenting him a medicine; to his left the devil is blowing sounds of hypochondric hallucinations in his ear. At the lower left, the black hellebore flower (containing toxic saponines and the narcotic poison helleborine) is shown as a remedy for depression (the description of the copperplate print is given in Geiger's book).



§. 504.

Mit dieser schwachen Wirkung der Reizbarkeit und Empfindlichkeit ist auf der andern Seite eine unordentliche Erregung dieser Kräfte und die mannigfaltigste Täuschung der Sinne verbunden. Der Melancholische schläft nie ganz ruhig: er fährt sehr oft aus dem Schlafe auf: hat die schreckhaftesten Träume, und beim Einschlafen Anfälle von Wahnsinn, und fühlt sich des Morgens mehrentheils müder als am Abend. Gewöhnlich klagt er über fürchterliche Kopfschmerzen in einer bestimmten Stelle des Kopfes, besonders im Hinterhaupt, mit dem Gefühl von Kälte und Betäubung verbunden. Nehmen die Kopfschmerzen sehr zu, so pflegt ein Anfall von Wuth bevorzustehn. Auch öftere Kolikschmerzen, die denen

ähnlich

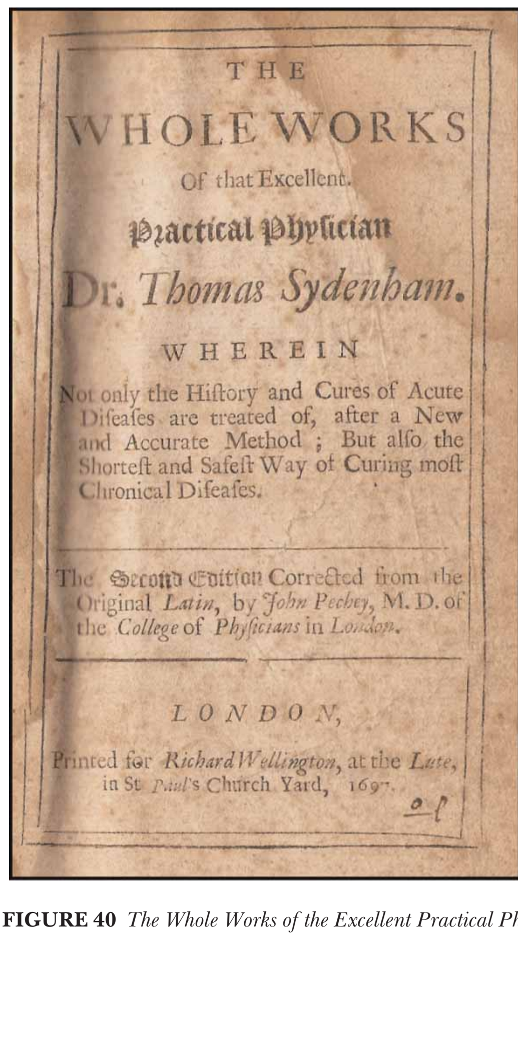
FIGURE 38 Sleep disturbance in a depressed patient. Sprengel *Handbuch der Pathologie*. Leipzig, Kühnsche Buchhandlung, p. 309 (Sprengel, 1810, pp. 135,136, 230, 231).

> *Die beobachteten Veränderungen dürften auch kaum durch den einfachen Mangel an Licht ausreichend erklärt sein. Von besonderer Wirksamkeit dürfte vielmehr die Veränderungen des Lichtrhythmus sein.*

FIGURE 39 Marx's *Zur Klinik des Hypophysenzwischenhirnsystems. 2. Mittelung Hypophysäre Insuffizienz* (Marx, 1946).

BIRTH AND DEATH

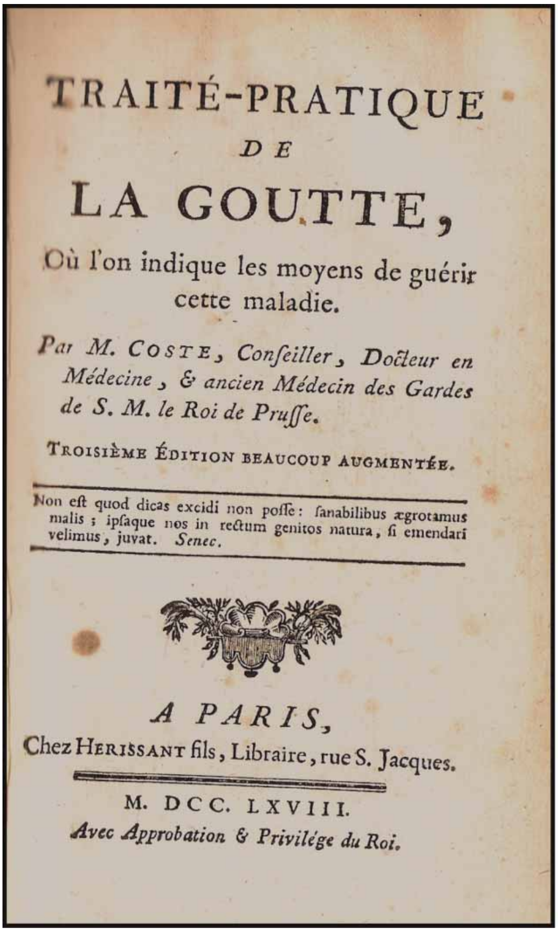
Alain Reinberg (1998) previously reviewed the ancient tale of *Nyx*, the Greek goddess of the night. Nyx, a daughter of Zeus, is usually presented while breastfeeding her two twins, Hypnos (translation: sleep) and Thanatos (translation: death). Thanatos is presented with open eyes and Hypnos with closed eyes. This means that some 2400 years ago, our Greek ancestors had observed and believed in a kind of phase relationship between sleep and death during the night hours. This phase relation between sleep and


THE
WHOLE WORKS
Of that Excellent
Practical Physician
Dr. *Thomas Sydenham*.
WHEREIN
Not only the Hiftory and Cures of Acute Difeafes are treated of, after a New and Accurate Method ; But alfo the Shorteft and Safeft Way of Curing moft Chronical Difeafes.
The Second Edition Corrected from the Original *Latin*, by *John Pechey*, M. D. of the *College* of *Phyficians* in *London*.
LONDON,
Printed for *Richard Wellington*, at the *Lute*, in St *Paul*'s Church Yard, 1697.

A Treatise of the Gout and Dropsie

There are thousand fruitful endeavours to ease the pain, ... yet there is no ease to be had, till two or three a clock in the morning at which time the sick has suddenly ease ...; ... yet the pain always returns in the vening, and is not so

FIGURE 40 *The Whole Works of the Excellent Practical Physician Dr. Thomas Sydenham* (Sydenham, 1697).

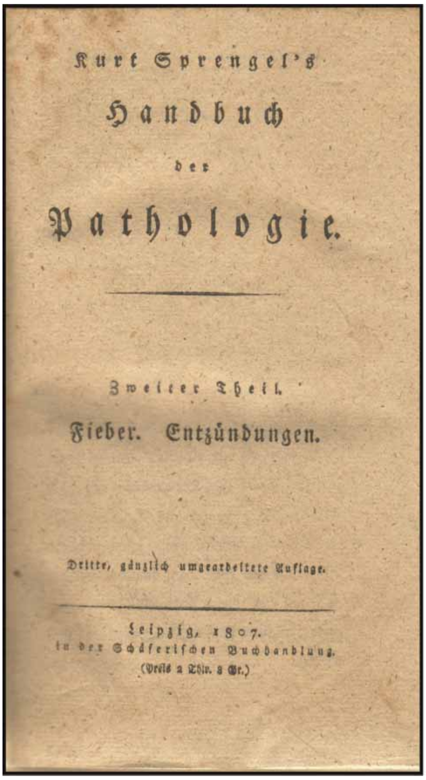

TRAITÉ-PRATIQUE
DE
LA GOUTTE,
Où l'on indique les moyens de guérir cette maladie.
Par M. COSTE, Conseiller, Docteur en Médecine, & ancien Médecin des Gardes de S. M. le Roi de Prusse.
TROISIÈME ÉDITION BEAUCOUP AUGMENTÉE.
Non est quod dicas excidi non posse: sanabilibus ægrotamus malis; ipsaque nos in rectum genitos natura, si emendari velimus, juvat. Senec.
A PARIS,
Chez HERISSANT fils, Libraire, rue S. Jacques.
M. DCC. LXVIII.
Avec Approbation & Privilége du Roi.

Ces douleur augmentent quelque fois si vite, que du matin aux soir l'accès est dans toute sa violence;…

FIGURE 41 Daily variation in the symptoms of gout as described by Coste in *Traité-Pratique de La Goutte* (Coste, 1768).

death is the basis of observations made centuries later through recordings and epidemiological studies on the time of death. Beginning in the 17th century, it was common practice to record the date and clock times of births and deaths in parishes and some city registries. Some of these registries can still be located; however, much of this interesting information unfortunately has been lost because of the destruction of books and public records during wars in Europe, mainly during the 30 Years' War (1618–1648).

Both the beginng and end of life do not occur at random times during the 24 h of the day or the month and season of the year. In 1972, Smolensky et al. published a detailed review on daily and seasonal patterns in birth and death by reanalyzing previously reported data and summarizing them on a population basis (Smolensky et al., 1972). However, credit is due to much earlier investigators for their


Kurt Sprengel's
Handbuch
der
Pathologie.
Zweiter Theil.
Fieber. Entzündungen.
Dritte, gänzlich umgearbeitete Auflage.
Leipzig, 1807.
in der Schäferischen Buchhandlung.
(Preis 2 Thlr. 8 Gr.)

Gicht:
Entweder am Tage, oder größtentheils zur Nachtzeit, nach dem ersten ruhigen Schlaf, bricht ein äußßerst heftiger, brennender Schmerz in den Gelenken der Fußwurzel, am äußseren oder inneren Knöchel, in den sogenannten Ballen der großen Zeehe .... aus.

FIGURE 42 Daily pattern in the symptoms of gout described in Sprengel's *Handbuch der Pathologie*, second part, Schäfersche Buchhandlung, Leipzig (Sprengel, 1810, p. 125).

observations and reports of such temporal patterns. Virey's thesis in 1814 included a table on the time of day of deaths occurring over a 13-month span in Paris (May 1807 to May 1808). The peak number of deaths was in the late night/early morning hours (Virey, 1814, p. 31). This result corresponds to the findings of Smolensky et al. (1972). Figure 44 shows the houly totals based on Virey's data along with the best fitting composite cosine curve approximation to his time series data. Table curve SPSS and cosinor time series analytical programs revealed a statistically significant 24 h variation, with the absolute peak revealed at 6 a.m. (Reinberg et al., 2001).

Das Rheumatische Fieber.
Das Fieber erneuert sich gewöhnlich alle Abende, doch pflegen die Anfälle einen Tag um den andern stärker zu sein.

FIGURE 43 Daily pattern in the symptoms of rheumatic fever as described by Sprengel (1807).

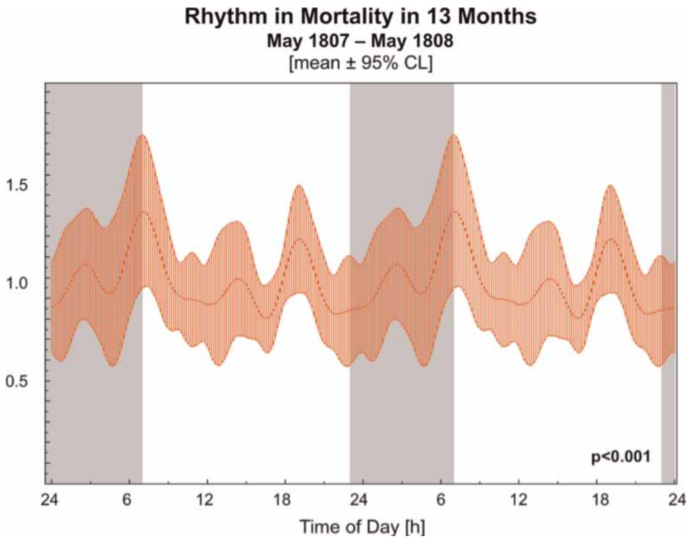
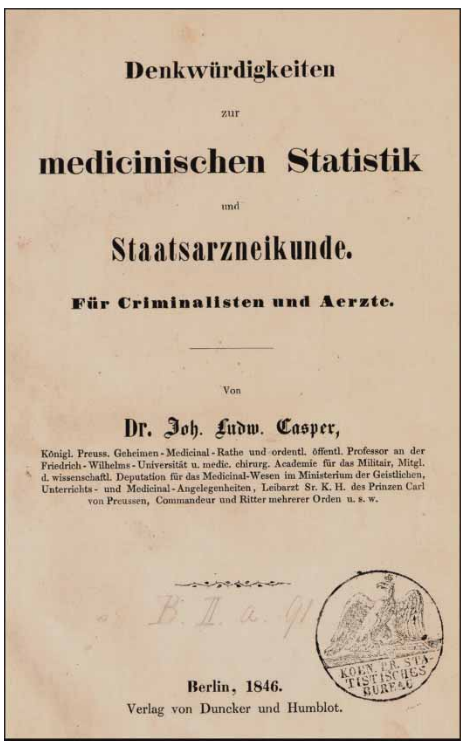


FIGURE 44 Virey's data (repeated plotted across two consecutive 24 h spans) on the time of day of deaths (Virey Thèse, Université de Paris, 1814). The absolute peak is found around 6 o'clock. Data were recalculated and analyzed by the author using Chronos-Fit (Zuther & Lemmer, 2004).



Denkwürdigkeiten

zur

medicinischen Statistik

und

Staatsarzneikunde.

Für Criminalisten und Aerzte.

Von

Dr. Joh. Ludw. Casper,

Königl. Preuss. Geheimen-Medicinal-Rathe und ordentl. öffentl. Professor an der Friedrich-Wilhelms-Universität u. medic. chirurg. Academie für das Militair, Mitgl. d. wissenschaftl. Deputation für das Medicinal-Wesen im Ministerium der Geistlichen, Unterrichts- und Medicinal-Angelegenheiten, Leibarzt Sr. K. H. des Prinzen Carl von Preussen, Commandeur und Ritter mehrerer Orden u. s. w.

Berlin, 1846.
Verlag von Duncker und Humblot.

FIGURE 45 Cover page of Casper's book, *Denkwürdigkeiten zur medicinischen Statistik und Staatsarzneikunde*, Publ. Duncker & Humblot, Berlin (Casper, 1846).

Detailed tables on the time of death from different causes, as well as birth, were also published by Johann Ludwig Casper (1796–1864) for the city of Berlin, Germany. Casper was a Professor at the University of Berlin and Royal Physician Councillor. In his book, *Denkwürdigkeiten zur medicinischen Statistik und Staatsarzneikunde*, he included 18th and 19th century data that he obtained from various sources. He also gathered his own data on thousands of patients in Berlin from 1833–1839 regarding the influence of time-of-day and seasonal variations (Casper, 1846). In addition, he presented data on seasonal variation in humidity. His book, containing numerous tables with detailed data, can be regarded as one of the first epidemiological treatises (see Figure 45). Casper's huge amount of data on mortality enabled him to conclude that a greater number of people die than expected during the early morning hours and that a lesser number than expected die during the hours before midnight: "*Das Maximum der Sterblichkeit fällt auf die Vormittags-, das Minimum auf die Vormitternachtsstunden*" (Casper, 1846, pp. 230ff). The data shown in the table of Figure 46 correspond to the findings of Smolensky et al. (1972). From his data on birth, Casper concluded that "*In den Stunden von 9 Uhr Abends bis 6 Uhr Morgens fallen die meisten, in die von 6 Uhr*

230 Der Einfluss der Tageszeiten

hier wie dort auf die Nachmittagsstunden. Das Uebergewicht der Zahl der nächtlichen über die Tages-Geburten ist hier also noch beträchtlicher als bei den lebend Gebornen, was wiederum für die oben aufgestellte Ansicht zur Erklärung der Thatsache spricht, dass die meisten Geburten des Nachts enden, da ja ein todtes Kind recht eigentlich ein dem mütterlichen Organismus fremd gewordener und schädlicher Körper ist.

Zweites Capitel.

Der Einfluss der Tageszeiten auf die Sterblichkeit.

Das Haupterforderniss medicinisch-statistischer Forschungen, zur Ermittelung allgemein-gültiger Naturgesetze, ist überall, neben der hinreichenden Anzahl der zu Grunde gelegten Thatsachen, dass letztere aus der Gesammtbevölkerung, nicht aber bloss aus einzelnen Klassen derselben entnommen seien, vorausgesetzt natürlich, dass nicht grade die einzelnen Klassen an sich Gegenstand specieller Untersuchung sind. In Bezug auf unsern Gegenstand ist es nun namentlich sehr wichtig, dass man nicht aus den vorgekommenen Todesfällen in Gefängnissen, Hospitälern u. s. w. Schlüsse über die allgemeine Sterblichkeit ziehe. Wir werden weiter unten Gelegenheit haben zu sehen, wie sehr die Sterblichkeitsverhältnisse in den einzelnen Tageszeiten bei verschiedenen Krankheitsklassen verschieden sind; nun ist es aber bekannt, dass grade gewisse Krankheiten in Hospitälern u. s. w. verhältnissmässig zu den übrigen Krankheiten viel häufiger vorkommen und also auch viel häufiger Todesursache werden, als dies in der Gesammtbevölkerung der Fall ist. Das Umgekehrte findet bei andern Krankheiten Statt, und so wird natürlich eine Untersuchung, wie die hier vorliegende, nur locale, nicht allgemeine Resultate geben, wenn sie sich auf die Ergebnisse der Krankenhäuser

Natürliche Krankheitsklassen mit den vorzüglichsten Krankheitsformen aus denselben	A Relative Zahlen der Gestorbenen in den Stunden				B Differenzen dieser Zahlen von dem Normalverhältniss				C	D
	v. 12-6 Nachts	v. 6-12 Morg.	v. 12-6 Nachm.	v. 6-12 Nachts	von 12-6 Uhr Nachts	von 6-12 Uhr Morgens	von 12-6 Uhr Nachmittags	von 6-12 Uhr Nachts	Verhältniss von Nacht zu Tag = 1 :	Verhältniss von Abend zu Morgen = 1 :
Chronische Krankh.	255	301	239	205	+ 3	+10	− 4	− 9	1,17	1,25
Schwindsuchten	225	290	260	225	− 27	− 1	+ 17	+ 11	1,22	1,06
Lungenschwinds.	220	294	263	223	− 32	+ 3	+ 20	+ 9	1,25	1,05
Unterleibsschwinds.	233	233	232	302	− 19	−58	− 11	+ 88	0,87	0,87
Atrophieen	257	309	228	206	+ 5	+18	− 15	− 8	1,16	1,30
Abzehrung d. Kinder	274	317	224	185	+ 22	+26	− 19	− 29	1,17	1,44
Altersschwäche	217	294	237	252	− 35	+ 3	− 6	+ 38	1,13	1,04
Blutflüsse	258	295	255	192	+ 6	+ 4	+ 12	− 22	1,22	1,23
Hirnschlagfluss	274	298	257	171	+ 22	+ 7	+ 14	− 43	1,24	1,33
Lungenschlagfluss	237	288	260	215	− 15	− 3	+ 17	+ 1	1,21	1,10
Chronische Catarrhe	281	322	233	164	+ 29	+31	− 10	− 50	1,24	1,51
Stickfluss	282	320	244	154	+ 30	+29	+ 1	− 60	1,29	1,51
Durchfälle	302	302	206	190	+ 50	+11	− 37	− 24	1,03	1,52
Wassersuchten	246	325	254	175	− 6	+34	+ 11	− 39	1,37	1,33
Allgemeine Wassers.	211	328	289	172	− 41	+37	+ 46	− 42	1,61	1,10
Brustwassersucht	260	333	226	181	+ 8	+42	− 17	− 33	1,27	1,45
Nervenkrankheiten	295	297	211	197	+ 43	+ 6	− 32	− 17	1,03	1,45
Krämpfe d. Kinder	295	297	213	195	+ 43	+ 6	− 30	− 19	1,04	1,45
Keuchhusten	309	274	167	250	+ 57	−17	− 76	+ 36	0,78	1,39
Sonstige chron. Krankh.	216	290	253	241	− 36	− 1	+ 10	+ 27	1,21	1,02
Herzkrankheiten	245	311	333	111	− 7	+20	+ 90	−103	1,81	1,24
Zahnung	202	282	242	274	− 50	− 9	− 1	+ 60	1,10	0,93
Drüsenkrankheit	291	273	218	218	+ 39	−18	− 25	+ 4	0,96	1,29
Organ. Unterl. Krkh.	182	236	327	255	− 70	−55	+ 84	+ 41	1,28	0,71
Normalverhältniss aus allen Todesfällen zusammengenommen	252	291	243	214	—	—	—	—	1,14	1,18

FIGURE 46 Tables from Casper's book, *Denkwürdigkeiten zur medicinischen Statistik und Staatsarzneikunde*, on the time of day in the ocurrence of death from various causes in Berlin (Casper, 1846).

Morgens bis 9 Uhr Abends die wenigsten Geburten" ("In the hours from 9 o'clock in the evening until 6 o'clock in the morning most births are given, whereas from 6 o'clock in the morning until 9 o'clock in the evening less births are given") (Casper, 1846, pp. 226 ff.; see Figure 47). Casper's book is highly exciting and a valuable source of information, and the detailed tabular data await further time series analyses!

The impact of time of the year on the number of births and deaths is well known, as comprehensively reviewed by Smolensky (1972). Figure 48 presents the seasonal pattern of births and deaths for the author's family ancestors based on records extending from 1450 to 2008. In spite of the fact that the "natural conditions" of environmental light have greatly changed as a result of the invention of electric lighting and widespread use of contraceptive methods within the last century, there is, nevertheless, strong evidence for seasonal patterning of both birth and death.

It is obvious that both the beginning—represented by the time of birth—as well as its termination—documented by the time of death—of life do not occur at random times, but display significant daily and seasonal variation.

Der Einfluss der Tageszeiten auf Geburt und Tod des Menschen.

Nichts ist Zufall!

Erstes Capitel.

Der Einfluss der Tageszeiten auf die Geburt.

Das Verhältniss, in welchem die Geburten zu den Tageszeiten stehen, ist ein Gegenstand, welcher erst in der neusten Zeit zu genauern Untersuchungen Anlass gegeben hat, nachdem schon ältere Lehrbücher der Geburtskunde, nach den bloss individuellen Erfahrungen ihrer Verfasser, die Frage obenhin berührt hatten*). Tiefer eingehend und nach einer grössern Reihe von Fällen (statistisch) gewürdigt haben ihn erst neuerlichst Ranken, Quetelet und Buek, und obgleich die Einzelnheiten ihrer Angaben verschieden sind, so stimmen sie doch alle darin überein, dass des Nachts mehr

*) Osiander, Handbuch der Entbindungskunst. Zweite Auflage. Tübingen 1830. Bd. 2. S. 42. Froriep, Theoretisch-practisches Handbuch der Geburtshülfe. Achte Ausgabe. Weimar 1827. § 218. Vict. Ad. Riecke's Beiträge zur geburtshülflichen Topographie von Würtemberg. Tübingen 1827. S. 6. Busch's Lehrbuch der Geburtskunde. Zweite Auflage. Marburg 1833. S. 5.

auf Geburt und Tod des Menschen. 227

Stunden des Eintretens der ersten Geburtswehen	Absolute Zahlen								
	Knaben		Mädchen		Knaben	Mädchen	Erstgeburten	Mehrgeburten	In Allem
	Erstgeburten	Mehrgeburten	Erstgeburten	Mehrgeburten					
Von 12-3 Morgens	31	24	32	32	55	64	63	56	119
„ 3-6 „	25	17	29	25	42	54	54	42	96
„ 6-9 „	25	18	16	20	43	36	41	38	79
„ 9-12 „	26	20	24	17	46	41	50	37	87
„ 12-3 Nachm.	26	15	20	21	41	41	46	36	82
„ 3-6 „	25	26	21	21	51	42	46	47	93
„ 6-9 Abends	33	20	41	19	53	60	74	39	113
„ 9-12 „	32	30	39	17	62	56	71	47	118
	223	170	222	172	393	394	445	342	787
„ 12-6 Morgens	56	41	61	57	97	118	117	98	215
„ 6-12 „	51	38	40	37	89	77	91	75	166
„ 12-6 Abends	51	41	41	42	92	83	92	83	175
„ 6-12 „	65	50	80	36	115	116	145	86	231
	223	170	222	172	393	394	445	342	787
	Relative Zahlen								
„ 12-3 Morgens	139	141	144	186	140	163	142	164	152
„ 3-6 „	112	100	131	145	107	137	121	123	122
„ 6-9 „	112	106	72	116	109	91	92	111	100
„ 9-12 „	117	117	108	99	117	104	112	108	110
„ 12-3 Nachm.	117	88	90	122	104	104	103	105	104
„ 3-6 „	112	153	94	122	130	107	104	137	118
„ 6-9 Abends	148	117	185	111	135	152	166	114	144
„ 9-12 „	143	178	176	99	158	142	160	138	150
	1000	1000	1000	1000	1000	1000	1000	1000	1000
„ 12-6 Morgens	251	241	275	331	247	300	263	287	274
„ 6-12 „	229	223	180	215	226	195	204	219	210
„ 12-6 Abends	229	241	184	244	234	211	207	242	222
„ 6-12 „	291	295	361	210	293	294	326	252	294
	1000	1000	1000	1000	1000	1000	1000	1000	1000
Tag : Nacht = 1 :	1,18	1,15	1,75	1,18	1,17	1,46	1,43	1,14	1,31
Morg. : Abd. = 1 :	1,12	1,15	1,19	0,83	1,11	1,02	1,14	0,97	1,06

15*

FIGURE 47 Table from Casper's book, *Denkwürdigkeiten zur medicinischen Statistik und Staatsarzneikunde*, on the time of day of girl's and boy's birth in Berlin (Casper, 1846).

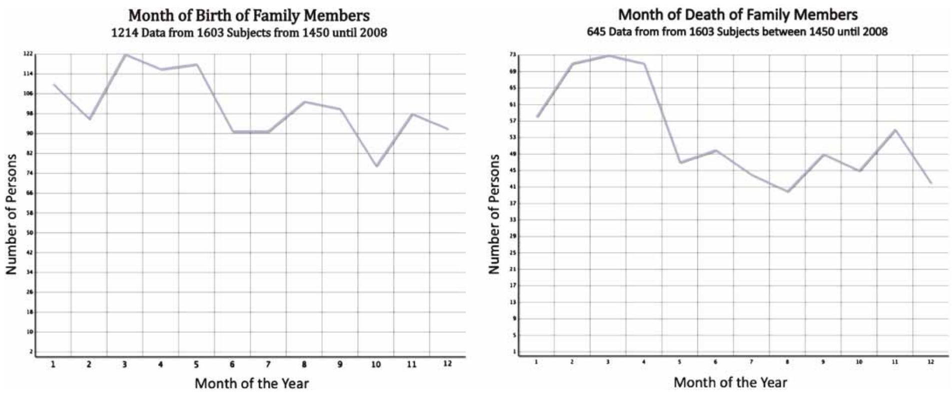


FIGURE 48 Month of birth and month of death of members of the author's family based on data available from 1450–2008. Data were assembled by use of MacFamilyTree (unpublished, the author's own family; Lemmer, 2009).

CONCLUSIONS

Though there are very early observations on temporal (e.g., 24 h and seasonal) variation in physiological and pathophysiological functions, such as on bronchial asthma by Caelius Aurelianus in the 5th century (Aurelianus, 1722), whose work was based on reports of Soranus from Ephesus who lived in the 2nd century, more detailed and more scientific reports were published beginning in the 17th century. It was the aim of this review to bring these early reports to the attention of both young and seasoned researchers in the field of chronobiology and chronopharmacology.

In this review, the author has referenced ancient books that he collected over time and are now a part of his personal library. The major intent of this review has been to demonstrate that chronobiology and chronopharmacology are not only modern branches of science, but that they have prominent roots in the past. From the number of books published since the 17th century, it is obvious that the mind and mental atmosphere during the Age of Enlightenment greatly stimulated physicians and other curious-minded individuals to observe and study in detail many diverse phenomena of life in plants, animals, and man. Sanctorius Sanctorius is regarded as the first physiologist who quantified his observations through performing experiments to measure respiration and weight. We have to take into consideration that the modern science of chronobiology stands on the shoulders of the wonderful observations and explanations of our scientific forefathers. As scientists, we should be modest and appreciate what has been discovered and presented in the last centuries. It is remarkable how many of the early observations and discoveries, especially relating to the symptoms of disease and invention of diagnostic devices—as mentioned in the paragraphs at the end of each of the sections—have been incorporated into clinical medicine and/or further developed in modern times. It is therefore concievable to state that physicians and scientists during the Age of Enlightenment paved the way to modern medicine, and, in particular, modern medical chronobiology and chronopharmacology.

Another point of this review has been to underline that a "modern" kind of publication politics, which insists on only English references in English-language journals—as exemplified by the Nature Publishing Group (Lemmer & Middeke, 2008)—is neither correct nor adequate for a scientific journal. This policy not only neglects scientific highlights of the past but other important contributions found in publications by scientists produced in other languages. It is the hope of the author that the reader will enjoy the richness of ancient reports that continue to contribute to our present knowledge of biological rhythms and the underlying research.

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