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Chapter 1

History of sleep medicine

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Sleep; King of all the gods and of all mortals, hearken now, prithee, to my word; and if ever before thou didst listen, obey me now, and I will ever be grateful to thee all my days (Homer, 14th book of the Iliad: *Mueller, 1984).*

Only a few physiological conditions have received as much attention from poets, novelists, scholars, and scientists as sleep. Writers from Aristotle and Ovid to Shakespeare and Dante have been fascinated by sleep and its impact upon our emotions, behavior, and health. Causes and reasons for sleep have been pondered by some of the world's greatest minds. Regardless of what the reason is, it is likely that sleep and dreams developed in animals because they were of some evolutionary benefit. Not only has sleep evolved through the ages but the environment for sleep has also undergone a change. From communal sleeping rooms with beds of twigs, straw, or skins, the bedroom has changed in the 21st century into a private place with electronic equipment, including remote-controlled television, DVD players, internet access, and even exercise equipment. The size of bedrooms has enlarged over the years.

A rudimentary understanding of insomnia and sleepiness was known in ancient times, but specific sleep disorders, such as narcolepsy, began to be recognized only in the late 19th century. Differentiation between causes of sleepiness and insomnia has reached a peak within the last 50 years since the development of sophisticated technology for the investigation of sleep.

Although most sleep disorders have probably been present since humans evolved, modern society has inadvertently produced several new disorders. The electric light bulb, developed by Thomas Edison, has allowed the light of day to be extended into night so that shift work can now occur around the clock, but at the expense of circadian rhythm disruption and sleep disturbance. Similarly, international jet travel has enabled the rapid crossing of time zones, which also can lead to a disruption of circadian rhythms and to sleep disturbance. Scientific investigation has produced more information on the physiology and pathophysiology of sleep in recent years than ever before. This rapid advance in sleep research and the development of sleep disorders medicine are producing answers to questions that date from antiquity.

SLEEP IN PREHISTORIC AND ANCIENT TIMES

Sleep's the only medicine that gives ease (Sophocles, Philoctetes*: Lloyd Jones, 1994).*

The sleep patterns and sleep disorders of prehistoric humans are unknown, and therefore we must speculate from the comparative physiology of animals and from evidence of other behaviors and illnesses. Theories on the phylogenetic development of sleep stages in mammals have been developed from information available on the mammal-like reptiles. The earliest form of life developed about 600 million years ago in the pre-Cambrian period, and mammal-like reptiles evolved approximately 250 million years ago. The monotremes (egg-laying mammals) evolved as a separate line from the therian (live-bearing) mammals about 180 million years ago. It is about this time when it is believed that slow-wave sleep appeared; rapid eye movement (REM) sleep (paradoxical sleep) appeared about 50 million years later. Recent sleep research on one of the three surviving monotremes, the Australian short-nosed echidna and platypus, has provided some of the evidence for the evolution of sleep stages. The monotremes have high-voltage REM sleep, which suggests that REM sleep may have had its origin in reptilian ancestors (Karmanova, 1982; Siegel et al., 1998).

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The pattern of sleep and waking behavior in prehistoric humans can be deduced from studies of animal groups phylogenetically closest to humans, namely nonhuman primates, such as apes and Old World monkeys. Sleep–wake patterns in nonhuman primates consist mainly of polyphasic episodes of rest and activity with frequent (up to 12) cycles of wakeful activity throughout the 24-hour day. Humans have the most developed monophasic pattern, with one episode of consolidated sleep and one main episode of wakefulness. Some animals, e.g., the chimpanzee, have a biphasic sleep–wake pattern, with a nap taken during the daytime. The chimpanzee has a rather prolonged sleep episode from dusk to dawn of approximately 10 hours; however, during this time there are frequent, brief awakenings. The daytime is characterized by two long episodes of wakefulness and an approximately 5-hour midday nap, which also includes frequent, brief wakefulness episodes. This type of sleep pattern may have the advantage of providing some security from predators.

Extrapolating from nonhuman primate studies, it seems likely that a similar polyphasic sleep pattern was likely to have been present in earliest humans (prior to the Neolithic period), particularly if they also attempted to sleep between dusk and dawn. There would have been frequent awakenings during the major sleep episode, as a single sleep episode of more than 10 hours appears unlikely. The monophasic sleep–wake pattern probably began in the latter part of the Neolithic period (since 10 000 BC). Neanderthal humans (70 000–40 000 BC) may well have been in a transitional stage between a polyphasic sleep pattern and the monophasic pattern seen today.

Prehistoric humans may have attempted to treat sleep disturbances, but how early they would have done this is unknown. Therapy probably resembled that utilized by sick animals, such as the removal of infective agents, eating various plants to induce emesis, and possibly even bloodletting. Bloodletting became an increasingly frequent therapeutic means for treating disease, including sleep disorders, in more advanced ancient civilizations. Primitive societies, even today, consider many illnesses and diseases to be caused by gods, magic, and spirits, and therefore various forms of divination, such as the casting of bones, moving of beads, charms, fetishes, chanting or the use of elaborate ceremonies, are invoked for therapeutic reasons. For disturbances of sleep and wakefulness, prehistoric humans probably applied similar forms of treatment.

Ancient Egypt

Most of our current knowledge of ancient Egyptian medicine derives from the ancient medical papyruses of Egypt (Ebbell, 1937). The Chester Beatty papyrus, which was written around 1350 BC, contains information on the interpretation of dreams. Dreams were regarded as being contrary predictions; for example, a dream of death meant a long life. However, an extensive text on a variety of medical subjects, including treatment, the Georg Ebers papyrus (1600 BC), has not been reported to contain any information on sleep disturbances. Ancient Egyptian medical practice consisted largely of praying to the gods and invoking the help of these divine healers. Thoth, who was a physician to the gods, and Imhotep were both important gods of healing at that time. The ancient Egyptians were known for their attention to hygiene and cleanliness, and it is likely that such attention was also paid to sleeping habits.

Medical opinion at the time held that the body was made up of a system of channels (Metu), which conveyed air to all parts of the body. Because they believed that bodily fluids could enter this system of channels, the ancient Egyptians were particularly concerned about feces entering the Metu. Hence, purging and enemas were the treatment modalities of many illnesses of that time, which included infective illnesses, such as malaria, parasitic infections, smallpox, and leprosy. Wine and other mildly alcoholic drinks (as compared to distilled alcoholic products) were consumed in large amounts and were probably the earliest treatments for insomnia but also may have been important in its development. Medicinal plants were utilized, particularly the product of the opium poppy (*Papaver somniferum*), and hyoscyamine and scopolamine, derived from belladonna and nightshade (Gunther, 1959). The word "opium" is derived from the Greek word for "juice," as the drug is derived from the juice of the poppy. *Papaver somniferum* was coined at a much later date; *somniferum* was derived from the Latin word *Somnus* (the Roman god of sleep). In subsequent periods in history opium (laudanum) was widely used as a treatment for insomnia, and it is likely that it was used as far back as the Sumerian age. Accordingly, opium may have been the first hypnotic medication used. Another common treatment performed by the ancient Egyptians for a variety of ailments and illnesses was bloodletting. This was likely to have been used for sleep disorders, particularly for those disorders that produced excessive sleepiness or stupor.

Medical treatment by physicians was widely available during this time. In fact, the names of several hundred physicians have been documented in ancient Egypt. Herodotus (fifth century BC) wrote of the Egyptians:

> *Medicine with them is distributed in the following way: every physician is for one disease and not for several, and the whole country is full of*

> *physicians for the eyes; others of the head; others of the teeth; others of the belly, and others of obscure diseases (Grene, 1987).*

It appears likely that some physicians specialized in insomnia, and possibly even in disorders that produced excessive sleepiness. There certainly were physicians who specialized in dream interpretation, for example Artemidorus of Daldis, who wrote the major work on dreams, *Oneirocritica* (White, 1975).

Ancient India

Other civilizations, such as those of ancient India and China, developed around the same time. In India, as in Egypt, infective illnesses were common, and therefore physicians, who were largely from the Brahman or priestly caste, were viewed with great importance. Medical practice mainly consisted of magical and religious practices but also featured soundly based, rational treatments. Over 700 Indian vegetable medicines have been documented from ancient times and include the plant called *Rauwolfia serpentina* (reserpine). *Rauwolfia* was used for the treatment of anxiety (and is currently being used for hypertension in some parts of the world) among other disorders, and is likely to have been used to treat insomnia (its side-effects include drowsiness).

Ancient China

The ancient Chinese viewed sleep as a state of unity with the universe:

> *everything is one; during sleep the soul undistracted, is absorbed into the unity; when awake, distracted it sees the different beings (Chinese philosopher Chuang Tzu, 300 BC: Palmer et al., 2006).*

The ancient Chinese believed in the importance of the universe and environment in producing all things, including behavior and health. The basic principles of life were thought to derive from the interplay of two basic elements in nature, the active, light, dry, warm, positive, masculine yang, and the passive, dark, cold, moist, negative yin. The proportions of yin and yang determined the Tao (the way), which determined right and wrong, good and bad, health or illness. The basic yin–yang symbol is attributed to Fu Hsi (*c.* 2900 BC), who originated the concept of eight interacting conditions, the "Pa kua." The yin–yang has since become the symbol for sleep and wakefulness. (This yin–yang symbol has been adopted by the American Academy of Sleep Medicine as its emblem.) Chinese views on physiology were similar to those of the ancient Greeks; they also believed in a humoral system of physiology. The palpation of the pulse was important in the diagnosis of disease, as were the patient's symptoms, the patient's social and economic status, the weather, and particularly the patient's dreams, as well as the dreams of other family members. These were all taken into consideration to determine whether a patient had upset the Tao.

The most important medical compendium of the time was that produced by Yu Hsiung (*c.* 2600 BC), the *Nei Ching* (*Canon of Medicine*). There is a great deal of controversy over the authorship of this text. It mentioned five important methods of treatment: curing the spirit, nourishing the body, the administration of medications, treating the whole body, and the use of acupuncture and moxibustion (counterirritation by moxa, a combustible substance that is burned on the skin). Acupuncture and a modified form of moxibustion are used today for the treatment of insomnia and other sleep disturbances in traditional Chinese medicine. When these therapies were first established (at least since *c.* 2600 BC), it follows that they were most likely applied to sleep disorders as well. Massage and breathing exercises were also commonly employed for various reasons, in a manner similar to yoga – these are therapies regularly used today for the treatment of some types of insomnia.

In addition to acupuncture, moxibustion, massage, and breathing exercises, the ancient Chinese had a plethora of herbal medicines. Herbal medicines consisted of extracts of virtually anything available, including minerals and metals, animal-derived products, and waste products (Gunther, 1959).

Two of these herbal remedies are worth noting. One was ephedra (Ma Huang), which is believed to have been used for over 4000 years. It is a stimulant that contains ephedrine, derived from the horsetail plant and first described by the Red Emperor, Shen Nung (*c.* 2800 BC). Ancient Chinese physicians used it for the treatment of asthma, hayfever, and nasal and chest congestion. It is reasonable to believe that it may have been used for the treatment of other breathing disorders of sleep as well. The second common medicinal herb was ginseng (a man-shaped root), which was used for a variety of ailments, including pulmonary problems and gastrointestinal disorders. It is also thought to heighten vitality and reduce fatigue and sedation (its role in excessive somnolence due to many causes including sleep disorders is thus apparent). Acupuncture was widespread and is believed to have been developed by the Yellow Emperor (Huang Ti) around 2600 BC (Veith, 1949). Acupuncture and moxibustion were used for treating virtually every illness and symptom and therefore may well have been administered for sleep disorders.

Ancient Greece

Much of what we know about early Greek medicine is derived from the Iliad and Odyssey of Homer, a collection of traditions, legends, and epic poems. Homer (*c*. 900 BC) based his epic works on the life of the ancient Greeks in the days of the Mycenaean Citadel of about 1200 BC. The Mycenaeans, who came from mainland Greece about 1600 BC, conquered the Minoans, who had established a well-developed civilization in Crete at Knossus. This civilization was the setting for Homer's epics, which concerned an earlier period, but his writings included medical details that were probably derived from his own era. However, Homer's view of medicine in early Greece, called homeric medicine, is the best representation of early Greek medical practices. The quotation from the *Iliad* stated at the beginning of this chapter reflects the importance that Homer ascribed to good-quality sleep. The god of sleep, Hypnos, from whom the terms hypnotic and hypnotism have derived, was first reported in the 14th book of the *Iliad* by Homer, and was mentioned again in the *Theogony of Hesiod* (*c*. 700 BC) about two centuries later (Wittern, 1989).

Also mentioned in Homer was the chieftain Asclepios and his two sons, Machaon, who in subsequent centuries became known as the father of surgery, and Podalirios, the father of internal medicine (Figure 1.1). In subsequent years, Asclepios became known as the god of healing, and temples were erected in his honor, the first being established about the sixth century BC in Thessaly or Epidauros. The Asclepieian temples were a collection of several buildings that in many cases were very elaborate and ornate. They consisted of a tholos, a round building that contained water for purification, and a main temple, which were separated by a building called the abaton. The abaton was a most important structure as it was the site where ill patients were placed for a cure. The cure consisted of an "incubation" ceremony in which the cure took place in each worshipper's dreams. The medical ceremony began at dusk and the ill patient lay on a bed of skins to await a visit by Asclepios, the god of healing. During the night the priest would visit each patient and administer a treatment, which often consisted of medicines derived from animals such as snakes and geese. Upon awakening the next morning after dreaming of Asclepios, the patient was expected to have been cured. This treatment was clearly the forerunner of sleep therapy, which has been practiced through the ages until the present day, particularly in eastern countries. Although Asclepieian medicine was used to treat any type of illness, it was most effective for those of a psychological nature. Much of the healing was probably related to the impressive ceremony and the relaxation that occurred in conjunction with the setting. The priest-physicians instilled faith in the cures, not only to their patients but also to themselves. However, many attempted cures were in the realm of magic and fantasy.

Fig. 1.1. Asclepios.

A more rational style of medicine developed around the fifth century BC largely due to the influence of the Greek scientist-philosophers. Alcmaeon (fifth century BC), of the Crotona school of medical thought, concentrated on humans, and his basic belief was that health was harmony and disease was a disturbance of harmony (Freeman, 1966). He considered the brain essential for memory and thought, a notion that Aristotle, who believed that the mind resided in the heart, would reject 100 years later. Alcmaeon proposed what was probably the first theory on the cause of sleep, when he postulated that sleep occurred when the blood moved away from the surface of the body to the deeper vessels, including those going to the brain; withdrawal of blood from the brain and inner vessels was associated with waking. However, his major contribution to medicine was the detailed description of the optic pathways at the base of brain. His much more rational concepts of medicine have led some to consider him the first true medical scientist.

Around the time of Alcmaeon, a center of medicine was established in Sicily, and Empedocles (*c*. 493–443 BC) was credited with the original concept that all things are composed of four basic elements: water, air, fire, and earth (the importance of these four elements had been established earlier: Freeman, 1966). Empedocles believed that sleep occurs when the fire in the blood cools, thus separating one of the four elements from the others. He believed that illnesses were due either to separation of the four elements or to alterations in their balance. The principle of the balance of body humors, known as humoralism, became established medical doctrine around this time. Humoralism considered health to be due to the balance of four body fluids: blood, phlegm (water), yellow bile ("choler," secreted by the liver) and black bile ("gall," secreted by the spleen and kidneys). These fluids were usually seen during severe illnesses and disappeared when the crises were over.

> *In whatever disease sleep is laborious, it is a deadly symptom (Hippocrates,* Aphorisms II*: Adams, 1891).*

Hippocrates (460–370 BC), born on the island of Cos, has had more influence upon medicine than any other individual in history. He produced many of the basic tenets that underlie the practice of modem medicine. Hippocrates produced numerous works that are gathered under the title *Corpus Hippocraticum*, which comprises not only his own writings but also the writings of others of the time (Chadwick et al., 1978). His approximately 72 books covered all aspects of medicine, including medical ethics, and are most widely known for the hippocratic oath. In his writings, Hippocrates discussed not only his theory of the cause of sleep, but also made suggestions on the cause of dreams, which he considered to be of "medical" origin. Hippocrates stated that: "sleep is due to blood going from the limbs to the inner regions of the body."

This statement was based upon the recognition of the importance of the blood being warmed by the inner part of the body in order to produce sleep. Hippocrates also alluded to some diseases of sleep of the time when he spoke of epilepsy (which appear to be descriptive of sleep apnea and the non-REM arousal disorders):

> *I have known many persons in sleep groaning and crying out, some in a state of suffocation, some jumping up and fleeing out of doors, and deprived of their reason until they awaken, and afterward becoming well and rational as before, although they be pale and weak; and this will happen not once but frequently (Adams, 1891).*

Hippocrates believed that narcotics derived from the opium poppy could be useful in treatment; therefore, they were most likely applied to treat insomnia at that time. Other philosophers, such as Diogenes (*c*. 480 BC) and Heraclitus (*c*. 450 BC), believed sleep was an incomplete "humidification of the bodily soul" and death was the complete humidification.

Following these philosophers, Aristotle (384–322 BC), had an important influence upon medicine. He believed that dreams were important predictors of the future but proposed a theory of sleep based upon the effect of food ingestion (Hett, 1964; Wijsenbeek-Wijler, 1978). He proposed that food, once eaten, induced fumes that were taken into the blood vessels and then transferred into the brain where they induced sleepiness. The fumes subsequently cooled and returned to the lower parts of the body, taking heat away from the brain, thereby causing sleep onset. The sleep process continued as long as food was being digested.

Ancient Rome

Greek medicine began to develop in Rome around the time of Hippocrates. Atomism, the concept that all physical objects are comprised of atoms in an infinite number that undergo random motion, was first developed by Democritus of Abdera (*c*. 420 BC) and Leucippus of Miletus (*c*. 430 BC). Leucippus regarded sleep as a state caused by the partial or complete splitting-off of atoms. Democritus considered insomnia to be the result of an unhealthy diet and daytime sleeping as being a sign of ill health. Epicurus (*c*. 300 BC) revived the theory of atomism and wrote extensively on sleep and dreams, although his own works have been lost. The Roman poet Titus Lucretius Carus (*c*. 50 BC) wrote of the teachings of Epicurus on atomism, sleep, and dreams in a poem entitled "De rerum natura." In this poem, the loss of central control that leads to loss of peripheral muscle control and relaxation forms the foundation of a neural theory of sleep that took 2000 years to be expanded upon:

> *And so, when the motions are changed, sense withdraws deep within. And since there is nothing which can, as it were, support the limbs, the body grows feeble, and all the limbs are slackened; arms and eyelids droop, and the hams, even as you lie down, often give way, and relax their strength (*On the Nature of the Universe: *Lucretius, 1994).*

Asclepiades of Bithynia (*c*. 120–70 BC), another figure in Roman medicine, believed that the physician was more important in curing disease than was nature. He used the term "phrenitis" for mental illness and invoked treatment that consisted of hygiene, opium, and wine. He was also the first to popularize the tracheostomy as a treatment for upper-airway obstruction resulting in apnea.

The Greek philosopher and physician Galen (AD 129–*c*. 200) had a great impact on the development of medicine. Galen's detailed writings substantially contributed to the knowledge of anatomy and he also outlined the important elements of diagnosis and treatment (Siegel, 1973, 1976). He believed bloodletting was important in the treatment of many illnesses, but he also encouraged conservative treatments, such as diet, rest, and exercise. He also spoke about dream interpretations and utilized many herbal medicines, e.g. valerian for the treatment of insomnia. In both ancient Rome and ancient Greece the similarity between death and sleep was often emphasized.

> *Sleep and death, who are twin brothers (Homer,* Iliad*, c. 850 BC: Mueller, 1984).*

> *What else is sleep but the image of chill death? (Ovid,* Amores *11, 43 BC–AD 17: Simpson, 2001).*

Sleep in the Bible

Similarly, in the Bible, death was described as being similar to sleep in that it was God who caused people to awaken from sleep; without Him they would never wake (Psalms 76:6). However, death was also contrasted with sleep in the example of a dead girl, about whom Christ said, "the little girl did not die but she is sleeping" (Matthew 9:24; Mark 5:39; Luke 8:52). This may have referred to the fact that she could be resurrected from death as one is awakened from sleep.

The Bible also contains numerous references to sleep and dreams, which were largely regarded as being predictors of the future (but less significant than in previous eras) (Mackenzie, 1965). Dreams also played an important part in the Bible as a means of communication between God and mankind. The first book of the Bible, Genesis (28: 10–16), reports communication between Jacob and God:

> *And Jacob went out from Beresheeba, and went toward Haran.*

> *And he lighted upon a certain place, and tarried there all night, because the sun was set; and he took one of the stones of that place and put them for his pillows, and laid down in that place to sleep.*

> *And he dreamed, and behold a ladder set up on the earth, and the top of it reached to heaven: and behold the angels of God ascending and descending on it . . .*

> *And Jacob awaked out of his sleep, and he said, surely the Lord is in this place; and I knew it not.*

Many other examples of dreams are presented in the Bible, such as Joseph's dream to take Mary as his wife, his dream to flee to Egypt with his family, the dream that it was safe to return home, and the dream of the Magi.

Excessive sleeping was regarded as being unacceptable as it produced laziness and could subsequently lead to poverty.

> *Laziness causes a deep sleep to fall (Proverbs 6:9–11, 10:5, 19:15, 20:13, 24:33–34).*

SLEEP IN THE MIDDLE AGES AND THE RENAISSANCE

> *Long sleep at after-noones by stirring fumes*
> *Breeds Slouth, and Agues*
> *Aking heads and Rheumes (School at Salerno, Regimen Sanitatis Salernitanum, 1095–1224: McVaugh, 1980).*

The time from the fall of Rome in AD 476 until the fall of Constantinople in AD 1453 is often referred to as the Middle Ages, the first 500 years being the Dark Ages. Both Ages comprise the medieval period, the Age of Faith, a time when medicine was greatly influenced by the rise of Christianity.

With the spread of the word of Christianity, people were convinced that the day of judgement was about to come, and disease was considered to be God's punishment. Prayer and good deeds were considered to be important for cures and to prevent illness. Concern for "thy neighbor" led to the establishment of facilities for the care of the ill, most of which were run with religious motives. Medicine involved strong religious mysticism, and there was a loss of the rational, clinical observation and management of disease that had begun to develop in earlier years. Although superstition and magic swept the western world, some physicians such as Avicenna, with skill in observation and deduction, slowly advanced medical knowledge.

In the Muslim world, there was a similar religious approach to medicine. Although in Islam, disease was regarded as a punishment by Allah, hospitals in Muslim countries were very much better than those in the west because of their improved sanitation and better and more spacious facilities. At that time physicians were largely of the Christian and Jewish faiths, but Muslim practitioners gradually helped spread medicine in the east. The Persian Razi (850–*c*. 923), also known as Rhazes in the west, wrote more than 200 books on many topics, including medicine (Ranking, 1914). Avicenna (980–1037 AD), who also contributed to medical understanding, was regarded both in Islam and Christendom as being of equal importance to Galen (Gruner, 1930, 1970). Included among his many contributions to medicine are the associations between epilepsy and insomnia and sleep deprivation.

In the latter part of this era, Moses ben Maimon (1135–1204 AD), also known as Maimonides, emerged as the most influential Jewish physician in Arabic medicine. He appeared to combine the thoughts of Hippocrates, Galen, and Avicenna but his primary focus was on philosophy. Maimonides had his own view of how much and when a person should sleep:

> *The day and night consist of 24 hours. It is sufficient for a person to sleep one third thereof which is eight hours. These should [preferably] be at the end of the night so that from the beginning of sleep until the rising of the sun will be eight hours. Thus he will arise from his bed before the sun rises (Mishneh Torah, Hilchoth De'oth, ch. IV, no. 4).*

In the 10th century AD, several medical schools came into prominence. Perhaps the first was that established at Salerno, not far from Monte Cassino. The school at Salerno developed a practical scientific approach to medicine, eschewing its neighbors' concentration on philosophy and religious mysticism. Several universities in France, including those at Montepellier and Paris, were also highly regarded. At Paris, the school had a medical rather than a surgical bias, being more influenced by the church. At Montpellier, Greek practices were more in evidence.

By AD 1000, at the end of the Dark Ages, monastic medicine began to decline as the influence of the universities increased. Many hospitals developed that are well known today, such as St. Thomas's and St. Bartholomew's in England and the Hôtel-Dieu in Paris. Diet was regarded as an important form of treatment, as were medications, particularly those derived from plant materials. One of the most commonly used medications at this time was theriac, which had been developed in the first century AD; it consisted of many substances derived from plants and animals, including snake flesh. Theriac would have been used for the treatment of a variety of sleep disorders, particularly those thought to be caused by poisons. Mysticism and astrology were important elements of medicine in the Middle Ages. Often the most important treatment to be considered was exorcism; however, purgatives and bloodletting were treatments that were still commonly employed.

In the 15th and 16th centuries, the works of Hippocrates were revived. Paracelsus (1493–1541), known as the father of pharmacology, began using metals in treatment, often producing some outstanding cures (Pachter, 1951). Although illnesses such as leprosy and the plague had largely disappeared, venereal diseases such as gonorrhea and syphilis were rampant. Paracelsus created a remedy that he believed to be "superior to all other heroic remedies" which he called laudanum. Laudanum was originally an extract of opium with brandy combined with other seemingly random ingredients, such as frogspawn. Among other purposes, this potion was used to induce sleep.

Art and medicine became allied, as evidenced in the anatomical drawings of Michelangelo Buonarroti (1475–1564) and Albrecht Dürer (1471–1528). Andreas Vesalius (1514–1564) produced one of the greatest medical books in history, *De Humani Corporis Fabrica* (O'Malley, 1965). Its detailed anatomical drawings surpassed those of Galen and Fabricius, and it became the anatomical cornerstone of scientific medicine in the centuries to come.

SLEEP IN THE 17TH AND 18TH CENTURIES

> *Methought I heard a voice cry, "Sleep no more!*
> *Macbeth does murder sleep," the innocent sleep,*
> *Sleep that knits up the ravell'd sleeve of care,*
> *The death of each day's life, sore labour's bath,*
> *Balm of hurt minds, great nature's second course,*
> *Chief nourisher in life's feast (Shakespeare:* Macbeth*, Act II,* c.*1605: Coursen, 1997).*

In the 17th century, medicine underwent a major change from the doctrines that had influenced it up to that time, such as aristotelianism, galenism, and paracelsianism, to more scientifically directed theories, with the underlying teleological desire to accumulate knowledge on the way things work. This time was known as the Age of Scientific Revolution and included the major medical developments of Francis Bacon, William Harvey, and Marcello Malpighi.

Medicine in general was now being viewed as an advancement in our control over nature and was more soundly based on scientific principles. However, it was still a time to be speculative and philosophical about medicine:

> *He sleeps well who knows not that he sleeps ill (Francis Bacon,* Omamenta Rationalia*, IV; quote from Publilius Syrus,* Sententiae*: Wight Duff and Duff Arnold, 1994).*

The scientific revolution began with the theories of René Descartes (1596–1650), who rejected Aristotle's doctrines and developed theories based on mechanisms (Descartes, 1632). In this regard he was similar to Francis Bacon (1561–1626), who espoused experimentation and utilitarianism. Descartes developed a hydraulic model of sleep, which considered that the pineal gland maintained fullness of the cerebral ventricles for the maintenance of alertness. The loss of "animal spirits" from the pineal causes the ventricles to collapse, thereby inducing sleep.

The chemical principles of Paracelsus were advanced in the 17th century, and medicines, including the use of mercurials, began to take over from treatments such as purging and bloodletting. Illness was now considered to be something that attacked the body in a distinct manner, and the galenic and earlier concepts that disease was a derangement of humors, the essential elements of the body, were starting to fade. Atomism, which had been proposed by Democritus, Leucippus, and Epicurus several centuries before the time of Christ, underwent a revival in the 17th century and was supported by the findings of Jan Baptista van Helmont (1577–1644), who coined the term "gas" and recognized that air was composed of a variety of gases. Robert Boyle (1627–1691) demonstrated the importance of air for life and the effect of gases under pressure, which led to the discovery that the reddening of venous blood occurred because of exposure of blood to gases contained in the air. However, the major discovery of the 17th century was that of William Harvey (1578–1657), who was the first to demonstrate that blood was pumped around the body by the heart.

It was against this background that the great neurologists, Thomas Willis (1621–1675) and Thomas Sydenham (1624–1689), developed the principles and practice of clinical neurology. Willis made a number of contributions to the knowledge of various disorders in sleep, including restless-legs syndrome, nightmares, and insomnia. He recognized that a component contained in coffee could prevent sleep and that sleep was not a disease but primarily a symptom of underlying causes. His book *The Practice of Physick* devoted four chapters to disorders producing sleepiness and insomnia (Willis, 1684). Like Descartes, he considered that the animal spirits contained within the body undergo rest during sleep. However, he believed that those animal spirits residing in the cerebellum became active during sleep to maintain a control over physiology. He believed that some of the "animal spirits" became intermittently unrestrained, leading to the development of dreams. He also described restless-legs syndrome, which he considered to be an escape of the animal humors into the nerves supplying the limbs:

> *when being abed, they betake themselves to sleep, presently in the arms and legs, leapings and contractions of the tendons, and so great a restlessness and tossings of their members ensue, that the diseased are no more able to sleep, than if they were in a place of the greatest torture (Willis, 1684).*

Willis also discovered that laudanum, a solution of powdered opium, was effective in treating the restless-legs syndrome.

Despite some setbacks, a scientific approach to medicine continued with the works of Linnaeus and von Haller. Karl von Linne (1707–1778), called Linnaeus, made important contributions to the classifications of botany, zoology, and medicine (Linnaeus, 1751). He emphasized the importance of cyclical changes in botany, which was nowhere more clearly presented than in his flower clock. The flower clock was developed upon the principle that different species of flowers open their leaves at various times of the day. Therefore, a garden of flowers arranged in a circular pattern could give an estimate of the time of day by the pattern of flower and leaf openings and closings. Linnaeus' finding was an important early milestone in the development of the science of biological rhythms in plants and animals. As far back as ancient Greece there had been some recognition of variation in the behavior of plants and animals, not only on a seasonal basis but also on a daily basis.

One of the first chronobiological experiments was that of Sanctorious (*c.* 1657), who measured the cyclical pattern of change in a number of his own physiological variables. His experimental apparatus has been regarded as the first "laboratory for chronobiology." Subsequently the intrinsic pattern of circadian activity was demonstrated in the experiment performed by Jacques de Mairan in 1729, which was reported by M. Marchant (de Mairan, 1729). De Mairan placed a heliotrope plant in a darkened closet and observed that the leaves continued to open in darkness, at the same time of day as they had in sunlight. This experiment illustrated the presence of an intrinsic circadian rhythm in the absence of environmental lighting conditions. De Mairan also recognized the importance of this observation for understanding the behavior of patients:

> *this seems to be related to the sensitivity of a great number of bed-ridden sick people, who, in their confinement, are aware of the differences of day and night.*

During the 17th and 18th centuries, medical schools had rapidly expanded throughout Europe, with those north of the French–Italian Alps beginning to gain in prominence. The Swiss-born scientist Albrecht von Haller (1708–1777), a pupil of Boerhaave of the University of Leiden, an important medical center in Europe, made major contributions to many scientific topics, including medicine. Von Haller performed numerous experiments on the nervous system and demonstrated the sensitivity of nerve and the irritability of muscle; in doing so he dispelled much of the mysticism of previous eras. Von Haller produced a major work entitled *Elementa Physiologiae* in which he devoted 36 pages to the physiology of sleep and proposed a theory for its cause (von Haller, 1766). In a vascular concept, similar to that of Alcmaeon in the fifth century BC, von Haller believed that sleep was caused by the flow of blood to the head, which induced pressure on the brain, thereby inducing sleep by cutting off the "animal spirits." Von Haller derived his beliefs from the views of his mentor Hermann Boerhaave (1667–1738). Von Haller's theory was expanded in the 19th century into the congestion theory of the causes of sleep, a theory that was still believed into the early part of the 20th century. He also considered dreams to be a symptom of disease, "a stimulating cause, by which the perfect tranquility of the sensorium is interrupted."

The late 17th century was also the time of the discovery of oxygen by Karl Scheele (1742–1786) and Joseph Priestley (1733–1804), but it was Antoine-Laurent Lavoisier (1743–1794) who coined the name "oxygen" and recognized its importance in the maintenance of living tissue. Despite the important advances in clinical medicine that occurred in the 17th century, there were very few therapeutic advances. Medications still consisted of potions developed from plant and animal tissues, and opium was still the main form of sedation, in a common formulation called "Hoffmann's anodyne of opium." The ancient practices of bleeding and purging continued to be widely prescribed throughout the 18th century.

It was not until the late 1700s that the greatest advance was made in the development of sleep medicine. It occurred in Bologna with Luigi Galvani's (1737–1798) demonstration of electrical activity of the nervous system. His findings led to the subsequent development of the field of electrophysiology, and the gradual destruction of the humoralist theory of nervous activity.

With the development of the scientific approach to medicine, the discovery of atomism, animal electrophysiology, the advances in respiratory and cardiovascular physiology, as well as treatment advances, such as quinine for malaria and digitalis for heart disease, medicine was about to enter its modern era, the 19th century.

SLEEP IN THE 19TH CENTURY

What probing deep
Has ever solved the mystery of sleep? (Thomas Aldrich (1836–1907), Human Ignorance*: Aldrich, 1876).*

The 19th century could be regarded as the "age of sleep theories" as some of the greatest physicians, psychologists, and physiologists turned their attention to explanations of the cause of sleep. Advances were made in the clinical recognition of sleep disorders, particularly the causes of daytime sleepiness, and several comprehensive books were written entirely on the physiological and clinical aspects of sleep. Much of what was known about insomnia and its causes, however, was only a slight expansion of earlier knowledge.

There were major advances in understanding the cause of sleep, and in the latter half of the century a number of specific sleep disorders were recognized. The anatomy of sleep and wakefulness was partially revealed through the animal experiments of two outstanding neuroanatomists of the time, Luigi Rolando (1773–1831) and Marie Jean Pierre Flourens (1794–1867).

Rolando in 1809 demonstrated that a state of sleepiness occurred when the cerebral hemispheres of birds were removed. His experiments were replicated by Flourens in 1824 with the ablation of the cerebral hemispheres of pigeons:

> *Just imagine an animal which has been condemned to be permanently asleep, one that has been devoid even of the ability to dream during sleep; this is more or less the situation of the pigeon in which I had ablated the cerebral hemispheres (Flourens, 1824).*

The theories of the cause of sleep can be placed into four main groups: vascular (mechanical, anemic, congestive), chemical (humoral), neural (histological) and a fourth group, which explains the reason for sleep rather than the physiological cause of sleep, the behavioral (psychological, biological) theories. The vascular theories of sleep were those most widely disputed in the early part of the 19th century. They were based upon the first rational theory for the cause of sleep, proposed by Alcmaeon in ancient Greece in the fifth century BC (Wittern, 1989). Alcmaeon believed that sleep is caused by blood filling the brain and waking associated with the return of blood to the rest of the body, a concept consistent with the notions of ancient times, when it was recognized that brain disorders such as apoplexy were associated with stupor (*karos*). Hippocrates had an alternative theory; he believed that sleep is due to blood flowing in the opposite direction, from the limbs to the central part of the body

(Chadwick et al., 1978, p. 8). Von Haller, in the 18th century, agreed with Alcmaeon's concept and proposed that blood going to the head causes the brain to be pressed against the skull, thereby inducing sleep by cutting off the "animal spirits." Von Haller derived his beliefs from the views of his mentor, Hermann Boerhaave (1667–1738), who had presented a similar theory a few years earlier, in 1750. These theories described the cause of sleep to be related to the blood vessels, either congestion (pressure of blood) in the brain or anemia (lack of blood) in the brain. Johann Fredreich Blumenbach (1752–1840), professor at Göttingen, who is regarded as the founder of modern anthropology, was the first to observe the brain of a sleeping subject in 1795 (Blumenbach, 1795). He noted that the surface of the brain was pale during sleep compared with wakefulness; contrary to earlier theories, he proposed that sleep was caused by the lack of blood in the brain. It was against this background of early sleep theories that the 19th-century researchers looked for the cause of sleep.

The theory that sleep was due to congestion of the brain was the most accepted vascular theory in the first half of the 19th century. Robert MacNish wrote a seminal volume on sleep and its disorders, entitled *The Philosophy of Sleep* (MacNish, 1830). MacNish supported the previous concept that sleep was due to pressure on the brain by blood. In 1846 Johannes Evangelista Purkinje (1787–1869), an outstanding neuroanatomist and professor of physiology and pathology at Breslau (Wroclaw, in modern Poland), proposed a slightly different theory for the cause of sleep that was consistent with the congestive concept (Purkinje, 1846; Kruta, 1967). Purkinje proposed that the brain pathways (corona radiata) become compressed by blood congestion of the cell masses of the brain (basal ganglia), thereby severing neural transmission and inducing sleep. James Cappie in 1872 wrote in detail about the circulation of the brain, and was one of the last supporters of the congestion theory. This theory was finally contradicted by the findings of the outstanding clinical neurologist John Hughlings Jackson (1835–1911). In 1863 Jackson observed the optic fundi during sleep and reported that the retinal arteries became pale during sleep, which was consistent with Blumenbach's earlier findings. He therefore reasoned that brain congestion was not a cause of sleep.

The main alternative to the congestion theory was that sleep was due to insufficient blood in the brain (anemia). William Alexander Hammond (1828–1900), the noted American physician, in 1854 was the first in the 19th century to direct attention to the anemia theory, after observing the brain of a patient who had a traumatic skull injury (Hammond, 1873, p. 31). In 1855, Alexander Fleming supported the anemia theory after he performed an experiment in which he occluded the carotid arteries and induced a sleep-like state. One of the strongest advocates for the anemia theory was Frans Cornelius Donders (1818–1889), a professor at Utrecht in Holland, who carefully observed the cerebral circulation in animals through windows placed in the skull (Donders, 1849). Donders and subsequently Angelo Mosso (1826–1910), who observed the cerebral circulation in humans with skull defects, believed that at sleep onset blood passed from the brain to the skin (Mosso, 1880). Arthur Edward Durham (1833–1895), who wrote extensively on the topic in 1860, believed that the blood passed from the brain during sleep not only to supply the skin but also to supply the internal organs (Durham, 1860).

One of the final advocates for the anemia theory of sleep was the physiologist William Henry Howell (1860–1945). Howell believed that the change in arterial blood pressure at the base of the brain was responsible for cerebral anemia (Howell, 1897). Sir Leonard Erskine Hill (1866–1952) extensively studied the cerebral circulation, and in 1896 reported the absence of a change in cerebral blood pressure during sleep (Hill, 1896). He believed that the brain did not become anemic or congested during sleep, and showed that intracranial pressure was normal during sleep compared with during wakefulness. By the end of the 19th century the vascular sleep theories, based on congestion or anemia of the brain, were less enthusiastically supported. Subsequent research showed that changes during sleep of both cerebral blood flow and intracranial pressure do occur, but it was no longer believed that these changes were responsible for the cause of sleep.

The neural theories for the cause of sleep were based upon mid-19th-century developments in the histological understanding of the central nervous system. Camillo Golgi (1843–1926) demonstrated the first clear picture of the nerve cell and its processes. His studies were extended by Heinrich Waldeyer (1837–1921), who first named the nerve cell – the neuron – and demonstrated an afferent axon and efferent dendrites. In 1890, Rabl-Ruckhardt developed a hypothesis, called "neurospongium," stating his belief that during sleep there was a partial paralysis of the neuron prolongations, which prevented communication with adjacent nerve cells. Subsequently, Raphael Jacques Lepine (1840–1919) of Paris in 1894 and Marie Mathias Duval (1844–1907) in 1895 proposed similar theories, agreeing that sleep was produced by retraction of ameboid processes of the nerve cell (Lepine, 1894; Duval, 1895).

The outstanding histologist Santiago Ramón y Cajal (1852–1934) proposed that small cells termed neuroglia interacted between neurons and were able to promote, or inhibit, the transfer of information from one cell to another. Cajal, who in 1906 was awarded the Nobel prize along with Golgi for his work on neurohistology, suggested that the alteration in the transference of information by neuroglia could explain not only sleep but also the effect of hypnotic medications (Cajal, 1895, 1952). Ernesto Lugaro proposed an alternative histological theory that sleep was due to expansion of the neuron processes (Lugaro, 1898). He believed that neural impulses inducing sleep passed through expanded processes (gemmules) to allow transmission between cells. (In the early 20th century, the theories relating movements to parts of the neuron were largely discredited and theories based upon synaptic transmission of neurotransmitters became the prominent neural explanation for changes of sleep and wakefulness.)

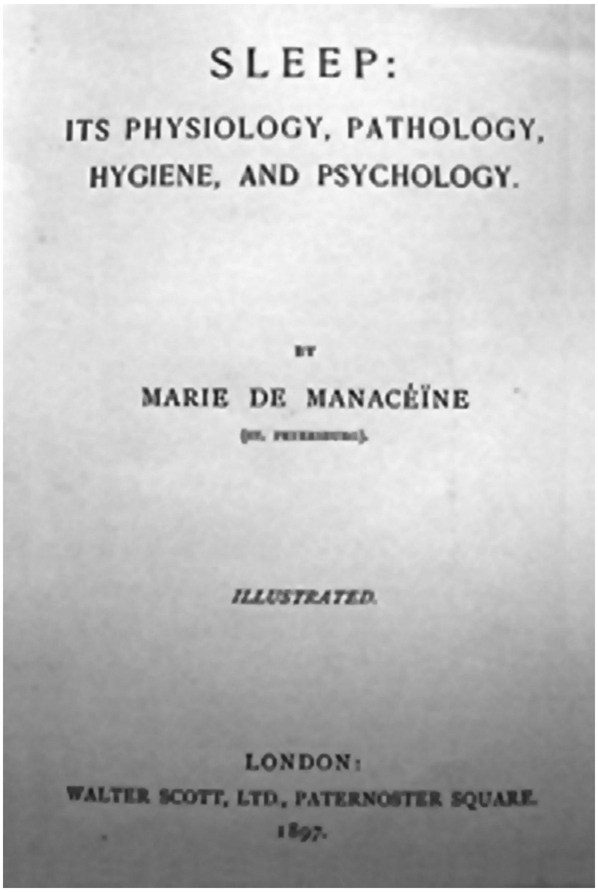
The chemical theories of sleep originated with Aristotle who believed that sleep was due to the effects of "fumes" taken into the blood vessels following the ingestion of food. Wilhelm Sommer in 1868 proposed that sleep was due to the lack of oxygen. Sommer's theory (quoted in de Manacéïne, 1897) was developed from the work of Carl von Voit (1831–1908) and Max Pettenkofer (1818–1901, who had shown in 1867 that the body absorbed more oxygen during sleep than during the day. Eduard Friedrich Wilhelm Pflüger (1829–1910) became the main advocate for the oxygen hypothesis in 1875 (Pflüger, 1875). Thierry Wilhelm Preyer (1841–1897) in 1877 believed that the accumulation of lactic acid during daytime fatigue led to a deficiency of oxygen in the brain at night, thereby causing hypoxemia and subsequent sleep (Preyer, 1877). This theory led to several others on the accumulation of toxic substances, which included cholesterol and other toxic waste products. Perhaps the most widely disseminated theory was that of Leo Errera of Brussels. Errera believed that the accumulation of poisonous substances called "leucomaines" induced sleep by passing from the blood to the brain (Errera, 1891). The leucomaines were believed to be gradually broken down during sleep, thereby leading to subsequent wakefulness. Raymond Emil Dubois (1818–1896) in 1895 proposed that sleep was a result of carbon dioxide toxicity, which in small amounts during wakefulness led to sleep (Dubois, 1895). Abel Bouchard (1833–1899) in 1886 proposed that sleep was due to toxic agents, excreted in the urine during sleep, that he called "urotoxins"; he also believed that diurnally produced urine contained toxic agents that produced wakefulness. The chemical theories continued to be popular at the end of the 19th century.

The behavioral theories of sleep developed from those of ancient times when general explanations were given for sleep. Although many behavioral theories were proposed over the years, the inhibition theory was the most popular. This theory, first alluded to in 1889 by Charles Edouard Brown-Séquard (1817–1894), and later expanded upon by Heubel and Ivan Pavlov, explained sleep as a process resulting from something being removed or inhibited in the brain.

Brown-Séquard, an outstanding clinical neurologist and physiologist, who believed that most glands had secretions that pass into the blood stream, is also known as the father of endocrinology. Based upon the previous work of Rolando (1809) and Flourens (1822), who had demonstrated that the removal of the cerebral cortex was accompanied by a sleep-like state (Flourens, 1824), Brown-Séquard (1852, 1889) proposed that sleep was due to an inhibitory reflex. The inhibitory theory of sleep was advanced with the experiment of Heubel, of Kiev University in Russia, who proposed that sleep was due to the loss of peripheral sensory stimulation, which was essential for the maintenance of alertness (Heubel, 1876). Subsequently, the inhibitory theory of sleep was greatly expanded by the work of Ivan Pavlov in the early 20th century (Pavlov, 1923, 1927). Marie de Manacéïne in 1897, in his book entitled *Sleep: Its Physiology, Pathology, Hygiene, and Psychology*, regarded sleep as being the "resting state of consciousness," which was an appealing truism, although it provided little information on the mechanism of sleep (de Manacéïne, 1897) (Figure 1.2).

A few researchers believed that a specific site in the body was capable of inducing sleep. The thyroid had been considered to be a sleep-inducing gland, until it was recognized that removal of the thyroid was not associated with insomnia. Jonathon Osborne in 1849 proposed that the choroid plexus was the "organ of sleep." He reasoned that congestion of the choroid kept the ventricles distended to produce sleep, and that contraction of the choroid was associated with wakefulness.

In the latter part of the 19th century two neurologists, Maurice Edouard Marie Gayet and Ludwig Mauthner, reported clinical findings that eventually led to the discovery of the brainstem's role in sleep and wakefulness. In 1875 Gayet presented a patient with lethargy and associated eye movement paralysis who had upper brainstem pathology at autopsy, which led Gayet to believe that the lethargy was due to a thalamic defect that produced impaired transmission from the brainstem to the cerebral hemispheres (Gayet, 1875). Mauthner in 1890 reported a similar association between an eye movement disorder and sleepiness but placed the site of the deficit at the brainstem level. These findings received little attention at the turn of the century because of the more popular vascular and chemical sleep theories.


SLEEP:

ITS PHYSIOLOGY, PATHOLOGY, HYGIENE, AND PSYCHOLOGY.

BY

MARIE DE MANACÉÏNE

ILLUSTRATED.

LONDON:
WALTER SCOTT, LTD., PATERNOSTER SQUARE.
1897.

Fig. 1.2. Title page of *Sleep: Its Physiology, Pathology, Hygiene, and Psychology* by Marie de Manacéïne (1897).

The science of chronobiology made a few advances in the 19th century, largely through the studies of plant biologists, such as Augustin Pyramus de Candolle (1778–1841), who demonstrated in 1832 that plants in constant conditions had a rhythm that differed slightly from 24 hours (de Candolle, 1832). Wilhelm Friedrich Phillip Pfeffer (1845–1920) in 1875 confirmed de Mairan's finding that plants had their own intrinsic rhythm when devoid of environmental influences. In 1845 James George Davey (1813–1895) reported circadian rhythms of his own core body temperature (Davey, 1858), and in 1866 William Ogle performed similar experiments:

> *There is a rise in the early morning while we are still asleep, and a fall in the evening while we are still awake, which cannot be explained by reference to any of the hitherto mentioned influences. They are not due to variations in light; they are probably produced by periodic variations in the activity of the organic functions.*

Although the theories regarding the cause of sleep were the focus of attention in the second half of the 19th century, important contributions were made to sleep disorders medicine. In 1869, Hammond, who was well known for his contributions to medicine during the Civil War, wrote a book based on his series of publications on insomnia, entitled *Sleep and its Derangements* (Hammond, 1873). Silas Weir Mitchell (1829–1914), a well-known and influential neurologist in America, wrote a number of clinical articles discussing the recognition of abnormal respiration during sleep, night terrors, nocturnal epilepsy, and the effect of stimulants on insomnia (Weir Mitchell, 1890).

Perhaps the greatest clinical contribution in the field of sleep disorders medicine was the first description in 1880 of narcolepsy by Jean Baptiste Edouard Gélineau (1828–1906), who derived "narcolepsy" from the Greek words *narkosis* (a benumbing) and *lepsis* (to overtake) (Gélineau, 1880). The term "cataplexy," for the emotionally induced muscle weakness (a prominent symptom of narcolepsy), was subsequently coined in 1916 by Richard Henneberg. Although Gélineau was the first to describe the clinical manifestations of narcolepsy clearly, several patients had previously been described by Caffe in 1862, Carl Friedrich Otto Westphal (1833–1890) in 1877 (Westphal, 1877), and Franz Fischer in 1878 (Fischer, 1878).

The leading sleep disorder of the 20th century, obstructive sleep apnea syndrome, was described in 1836, not by a clinician but by the novelist Charles Dickens (1812–1870). Dickens published a series of papers entitled *The Posthumous Papers of the Pickwick Club* in which he described an obese boy named Joe who was excessively somnolent, a loud snorer, and who probably had right-sided heart failure (thus earning the nickname "young dropsy": Dickens, 1836) (Figure 1.3).

> *Mr. Lowton hurried to the door... The object that presented itself to the eyes of the astonished clerk was a boy – a wonderfully fat boy standing upright on the mat, with his eyes closed as if in sleep. He had never seen such a fat boy, in or out of a traveling caravan; and this, coupled with the utter calmness and repose of his appearance, so very different from what was reasonably to have been expected of the inflicter of such knocks, smote him with wonder.*
>
> *"What's the matter?" inquired the clerk.*
>
> *The extraordinary boy replied not a word; but he nodded once, and seemed, to the clerk's imagination, to snore feebly.*
>
> *"Where do you come from?" inquired the clerk.*
>
> *The boy made no sign. He breathed heavily, but in all other respects was motionless.*

Fig. 1.3. Joe, the fat boy from *The Posthumous Papers of the Pickwick Club* by Charles Dickens (1836).

The clerk repeated the question thrice, and receiving no answer, prepared to shut the door, when the boy suddenly opened his eyes, winked several times, sneezed once, and raised his hand as if to repeat the knocking. Finding the door open, he stared about him with astonishment, and at length fixed his eyes on Mr. Lowton's face.

"What the devil do you knock in that way for?" inquired the clerk, angrily.

"Which way?" said the boy, in a slow, sleepy voice.

"Why, like forty hackney-coachmen," replied the clerk.

"Because master said I wasn't to leave off knocking till they opened the door, for fear I should go to sleep" said the boy.

More than 100 years followed Charles Dickens' description before the obstructive sleep apnea syndrome became a well-recognized clinical entity. However, a number of writers in the 19th century did allude to some of the features of sleep apnea in their publications. William Wadd, surgeon to the King of England, in 1816 wrote about the relationship between obesity and sleepiness. George Catlin, a lawyer, in 1872 described the breathing habits of the American Indian in his book entitled *The Breath of Life*; he graphically portrayed the effects of obstructed breathing during sleep (Figure 1.4). William Henry Broadbent (1835–1907) in 1871 was the first physician to report the clinical features of the obstructive sleep apnea syndrome, and William Hill in 1889 observed that upper-airway obstruction contributed to "stupidity" in children. The most notable description was by William Hughes Wells (1854–1919) in 1878; he cured several patients of sleepiness by treatment of upper-airway obstruction (Wells, 1878).

SLEEP IN THE 20TH CENTURY

The interpretation of dreams is the royal road to a knowledge of the part the unconscious plays in the mental life (Freud, 1958).

Sleep medicine advances in the 20th century were greatly affected by the development of new diagnostic means and the innovations in surgery. For the first time objective diagnostic procedures complemented the physician's skill. X-rays were discovered in 1895 by Wilhelm Konrad Roentgen (1845–1923) and the first clinical application was reported in 1896. Widespread routine use of X-ray procedures began in the early 20th century; sophisticated brain imaging techniques such as computed axial tomography and nuclear magnetic resonance scanning began in the second half of the century.

The vascular theories of the cause of sleep were no longer popular, and although the chemical theories

Fig. 1.4. Obstructed breathing during sleep. (Reproduced from Catlin (1872).)

were briefly of interest due to the findings of René Legendre and Henri Pieron in 1907 (Legendre and Pieron, 1907; Pieron, 1913), they were overshadowed largely by the behavioral theory of Ivan Petrovitch Pavlov (1849–1936). Pavlov, who is regarded as one of the greatest physiologists of all time, published his initial lectures on conditional reflexes in 1927 (Pavlov, 1927). There he expressed a belief that sleep was due to widespread cortical inhibition:

> *Sleep… is an inhibition which has spread over the great section of the cerebrum, over the entire hemispheres and even into the lower lying midbrain.*

Pavlov's studies on dogs showed that a continuous and monotonous stimulus would be followed by drowsiness and sleep. He reasoned that the continuous stimulus acts at a certain point of the central nervous system and leads to inhibition with resulting sleepiness. Although Pavlov's theories on conditioning were interesting, they held little information on physiological mechanisms. Vladimir Michailovich Bekhterev (1857–1927) published his findings on human reflexology and sleep in 1894 (translated into English in 1932). Bekhterev also believed that sleep was a general inhibition due to a loss of higher-level reflexes:

> *[Sleep is] a reflex which has been biologically evolved for the purpose of protecting the brain from further poisoning by the products of metabolism, and which may be evoked, as an association reflex, and the conditions of fatigue.*

Bekhterev's theory, similar to that of Edouard Claparède, who in 1905 viewed sleep as an "instinct," was subsequently influenced by the work of Legendre and Pieron; it proposed that the biochemical processes leading to the inhibition of the brain were "hypnotoxins." Since that time, electrophysiological studies have demonstrated that the passive, cortical inhibition proposed by Pavlov and Bekhterev does not occur; instead, the brain maintains its activity during sleep, particularly during REM sleep.

Dichotomy of sleep

Since the days of ancient Greece, it had been recognized that sleep consisted of two different states, one associated with dreaming and the other with quiet sleep. Willis in the 17th century had noticed the difference, and believed that dream sleep was associated with release of the "animal spirits" from the cerebellum. However, the physiological changes of dreaming sleep were not reported until 1868 when Wilhelm Griesinger (1816–1868) noted the associated eye movements. Sigmund Freud in 1895, before the publication of his first book on dreams in 1900, recognized that paralysis of skeletal muscles during dream sleep prevented the dreamer from acting out dreams (Freud, 1958).

Sleep research, both basic and clinical, had its greatest period of growth during the second half of the 20th century. The advances in neurochemistry, electrophysiology, neurophysiology, chronobiology, pathology of sleep, and sleep disorders medicine and the development of sleep societies are too numerous to list, but a summary is given below.

Neurochemistry

> *Our studies have established that the accumulation of the hypnotoxin produces an increasing need for sleep (Pieron, 1913).*

Although attempts to replicate the work of Legendre and Pieron on hypnotoxin were often unsuccessful, in 1967 John Pappenheimer and colleagues induced sleep with cerebrospinal fluid obtained from sleep-deprived goats. The transmissible chemical, called "factor S," was subsequently identified as a muramyl peptide in 1982 and is thought to act via the leukocyte monokine interleukin-1. Finding alternative sleep factors has met with mixed success; the number of putative sleep factors has grown enormously in the last 20 years. However, in 1988 Osamu Hayaishi discovered that prostaglandin PGD_2, found in the preoptic muclei, was capable of inducing sleep in rats, leading to the speculation that the preoptic nucleus is the site of the perennial and elusive "sleep center."

Hypocretin/orexin was discovered independently in 1998 by two separate groups of researchers. Luis de Lecea and Thomas Kilduff and colleagues from San Diego identified two peptides derived from a single gene in the hypothalamus that had a sequence homology to secretin that they called hypocretin (de Lecea et al., 1998). At the same time, Takeshi Sakurai and Akira Amemiya and colleagues also isolated these same peptides in Texas and named them orexin (Greek for appetite) (Sakurai et al., 1998). Both groups were not investigating sleep, but were searching for novel obesity treatments. Chemelli et al. further studied hypocretin/orexin in 1999 and discovered that loss of hypocretin produced symptoms in rodents that were similar to that of cataplexy and sleep attacks as seen in humans. Emmanuel Mignot and colleagues in 1999 determined that dogs with narcolepsy had a loss of hypocretin and subsequently it was shown that most human patients with narcolepsy and cataplexy had reduced or absent cerebrospinal fluid levels of hypocretin (Lin et al., 1999).

Electrophysiology

Feeble currents of varying direction pass through the multiplier when electrodes are placed on two points of the external surface [of the brain] (Caton, 1875).

The most useful objective diagnostic means for sleep disorders has proven to be electrophysiological techniques. Following Galvani's demonstration of the electrical activity of the nervous system in the late 18th century, Richard Caton (1842–1926) in 1875 demonstrated action potentials in the brains of animals, an important step in the development of the electroencephalograph (Caton, 1875). In 1929, Johannes (Hans) Berger (1873–1941), the first to record electrical activity of the human brain, demonstrated differences in activity between wakefulness and sleep. Berger's discovery led to the development of the electroencephalograph as a clinical tool for the diagnosis of brain disease. The electroencephalograph was applied to determine different sleep states in 1937, when Alfred L. Loomis, E. Newton Harvey (1887–1959), and Garret Hobart were able to classify sleep into five stages, from A to E (Loomis et al., 1935).

Dream sleep was characterized in 1953 by Eugene Aserinsky and Nathaniel Kleitman, who demonstrated the occurrence of rapid eye movements during the dreaming stage of sleep, that they called "rapid eye movement (REM) sleep."

The traditional manner of producing sleep studies by using polysomnographs that used ink and paper was rapidly replaced by digital systems after the year 2000. The death knell to paper systems came at the end of 2006 when the Grass P78 polysomnograph recording paper became unavailable.

In 1957 Kleitman and William Dement discovered a recurring pattern of REM sleep and non-REM sleep during overnight electroencephalographic monitoring – a finding that made it clear that sleep no longer could be regarded as a homogeneous state (Dement and Kleitman, 1957). In 1968, Allan Rechtschaffen and Anthony Kales developed a scoring manual, *A Manual of Standardized Terminology, Techniques, and Scoring System for Sleep Stages of Human Subjects*, which has become the standard in the field (Rechtschaffen and Kales, 1968). In 2007, a major revision of the traditional sleep-staging rules was developed by the American Academy of Sleep Medicine (Iber et al., 2007).

The first report of an effective measure of daytime alertness was by Gary Richardson et al., in 1978. This study compared narcoleptics with normal individuals by applying the Multiple Sleep Latency Test (MSLT) that had been conceived and developed by Mary Carskadon, working with William Dement at Stanford University:

analysis of hypnogenic mechanisms has thus underlined the paramount importance of inhibition and disinhibition in the deterrnination of sleep onset and maintenance – a striking illustration of Sherrington's visionary concepts (Bremer, 1977).

Neurophysiology

In the early part of the 20th century, two schools of thought emerged regarding the neurophysiological basis of sleep and wakefulness. One characterized sleep as due to disinhibition with release of an active "sleep center," and the other as due to a passive event, the result of inhibition of a "waking center." The theories, proposed at the end of the 18th century by Mauthner and others, assumed an interruption of peripheral sensory stimulation, thereby allowing the cerebral cortex to produce sleep. This "deafferentation" theory had been suggested first by Purkinje in 1846. The notion of a specific sleep center did not receive much support, as illustrated by the comment of the prominent clinical neurologist Jacques Jean Lhermitte (1877–1959) in 1910 (Lhermitte, 1910):

We absolutely object to the thought of the existence of a nerve center attributed to the function of sleep. The conception of a center for sleep is erroneous, as it disavows the most simple principles of physiology.

Lhermitte was supported in 1914 by a pioneer of brain localization, Joseph Jules Dejerine, who said, "Sleep cannot be localized" (Dejerine and Dejerine-Klumpke, 1914). However, in 1929, Constantin von Economo (1876–1931) proposed a "center for regulation of sleep" based on anatomical and clinical studies of "encephalitis lethargica" at the Psychiatric Clinic of Wagner von Jauregg in Vienna (von Economo, 1923, 1929a). Viral encephalitis reached epidemic proportions between 1916 and 1920, and von Economo had the opportunity to correlate the clinical features of sleep disturbance with the central nervous system pathology. His studies demonstrated inflammatory lesions in the posterior hypothalamus in patients with excessive sleepiness and lesions in the preoptic area and anterior hypothalamus in patients with insomnia (von Economo, 1929b). Von Economo, influenced by the studies by Pieron and Pavlov, suggested that the "sleep-regulating center" was controlled by substances circulating in the blood. These substances caused the sleep center to exert an inhibitory influence on the cerebral cortex, thereby leading to sleep. The same year in Zurich, Walter Rudolph Hess (1881–1973), who was awarded the Nobel prize with Egas Moniz for his work in neuroanatomy, confirmed von Economo's findings by demonstrating that stimulation of the central gray matter in the region of the thalamus induced sleep (Hess, 1944).

Kleitman in 1939 regarded the cerebral cortex as being the source of wakefulness, and believed that sleep due to inactivity of the central nervous system was brought about by a reduction in peripheral stimulation because of fatigue. His hypothesis conformed to the "deafferentation" theory. Steven Walter Ranson (1880–1942) in 1932 demonstrated that lesions placed at the top of the brainstem produced sleepiness; experimentally, this was consistent with von Economo's findings (Ranson and Ingram, 1932).

In 1935, Frédéric Bremer, of the University of Brussels, experimentally gave support to the deafferentation theory. Bremer completely transected the midbrain, producing the "cerveau isolé" preparation, an isolation of the cerebrum, and was able to show characteristic sleep patterns on the electroencephalogram. The studies up until this time were consistent with the concept that a lesion that prevented transmission of peripheral stimulation was important in the production of sleep. However, Ranson in 1939 showed that lesions of the lateral hypothalamus, in the absence of upper-brainstem lesions, were associated with sleep due to a loss of the "waking center." A few years later, Walle Jetz Harinx Nauta demonstrated that posterior hypothalamic lesions produced sleepiness whereas anterior hypothalamic lesions produced insomnia, thereby supporting the concept of a waking center in the posterior hypothalamus and a sleep center in the anterior hypothalamus (Nauta, 1946). According to Nauta:

> *Whereas Ranson and his collaborators held that periods of sleep were caused by more or less intrinsic periodic decreases in activity of the waking center, we are inclined to attribute these decreases to the inhibitory influence of a sleep center.*

Horace W. Magoun and Ruth Rhines, at the Northwestem University Medical School in Chicago, demonstrated in 1946 that the lower portion of the brainstem reticular formation was responsible for inhibiting skeletal muscle tone (Magoun and Rhines, 1946). This function of the lower brainstem had earlier been alluded to by the clinical studies of Jackson in 1898. That the lower reticular formation could have an inhibitory function through descending pathways led to Guiseppe Moruzzi and Magoun's finding in 1949 that the brainstem reticular formation also had ascending pathways (Moruzzi and Magoun, 1949; Moruzzi, 1964). This resulted in the discovery of the "ascending reticular activating system," which led to a new emphasis in the physiological investigation of sleep. Stimulation of the ascending reticular activating system produced electroencephalographic patterns of wakefulness. It was now recognized that the brainstem transection studies did not produce sleep because of "deafferentation" of peripheral sensory input, but because of the loss of the wakefulness stimulus from the ascending reticular activating system. As a result, sleep became regarded as a passive phenomenon.

At the beginning of the second half of the 20th century, research concentrated on determining the neurophysiological basis for non-REM and REM sleep. Following the electrophysiological documentation of REM sleep, Michel Jouvet and colleagues in 1959 demonstrated REM sleep-related muscle atonia, and in 1965 demonstrated that the brainstem serotonin-containing neurons of the raphe nuclei were important in sleep and wakefulness (Jouvet and Delorme, 1965). Subsequently, Jouvet demonstrated that the rostral raphe nucleus was important for non-REM sleep, whereas the caudal raphe nucleus was important in the maintenance of REM sleep. In 1975, Robert William McCarley and J. Allan Hobson proposed a reciprocal interaction model of REM and non-REM sleep, with rostral REM "on" cells and caudal REM "off' cells (McCarley and Hobson, 1975). In 1996 a small group of cells, called the ventrolateral preoptic nucleus, was discovered by Sherin to be an important sleep-generating nucleus that comes as close as any cell group to being a major "sleep center" (Sherin et al., 1996).

Chronobiology

> *Despite the multiplicity of its constituents, the circadian system often behaves like one unit which is characterized by the durability of its oscillations and its internal temporal order (Aschoff, 1981).*

Auguste Henri Forel (1848–1931), a Swiss physician, is credited with stimulating the investigation of circadian rhythms as important time-measuring systems. His studies in 1910 on the accurate timing system of bees were consistent with those of de Mairan in the 18th century on the opening of the flower petals at a given time of day. The circadian behavior of rodents was first reported by Curt P. Richter in his Ph.D. thesis in 1922; and Erwin Bunning in 1935 was able to demonstrate the genetic origin of circadian rhythms in plants and subsequently developed a concept of "biological clocks." In the early 1960s Richter searched for the biological clock in extensive studies that culminated with the report in 1965 that lesions placed in the anterior ventral hypothalamus produced disruption of circadian rhythms (Richter, 1965). Two groups acting independently in 1972, Robert Y. Moore and Victor

B. Eichler, and F.K. Stephan and Irving Zucker, discovered the "clock" to be two small, bilateral nuclei in the anterior hypothalamus, which were subsequently called the suprachiasmatic nuclei (Moore and Eichler, 1972; Stephen and Zucker, 1972).

Jules Aschoff and Kurt Wever investigated human circadian rhythms in the absence of environmental time cues in 1962 in an underground laboratory in Munich. They demonstrated a free-running pattern of sleep and wakefulness with a period length of greater than 24 hours.

A similar free-running pattern was demonstrated in field experiments (1964) by the speleologist Michel Siffre, who lived for 3 months in the absence of time cues on an ice glacier deep in the Franco-Italian mountains (Siffre, 1964). Many human biological rhythms have recently been discovered, such as the 24-hour episodic secretory pattern of cortisol that was reported by Elliot David Weitzman (1929–1983) in 1966 (Weitzman et al., 1966).

In 1980, Weitzman et al. demonstrated the internal organization of temperature, neuroendocrine rhythms, and the sleep–wake cycle in subjects who were monitored in an environment free of time cues for periods of up to 6 months. Sutherland Simpson (1863–1926) and J.J. Galbraith in 1906 had demonstrated that the light–dark cycle could influence mammal behavior. However, it was not until the 1980s that Czeisler and colleagues demonstrated the importance of the light–dark cycle in the entrainment of human circadian rhythms. The genetic basis for the control of circadian rhythms was established in 1971 by R. Konopka, initially in fruit flies but subsequently in humans (Konopka and Benzer, 1971). The recognition by K. Toh in 2001 that advanced sleep phase syndrome was associated with a genetic mutation of the human period gene two (h*Per*2) led to the recognition that alterations in timing of the sleep–wake pattern could be controlled by genetic factors (Toh et al., 2001).

Pathology of sleep

Five billion people go through the cycle of sleep and wakefulness every day, and relatively few of them know the joy of being fully rested and fully alert all day long (William Dement 1988).

Sleep disorders were poorly described at the turn of the century, and, other than narcolepsy and sleeping sickness (African trypanosomiasis), few specific sleep disorders were recognized. In addition to general medical illness, environmental effects and anxiety were viewed as the main causes of sleep disturbance. However, a gradual recognition of the multiplicity of sleep diagnoses began to parallel progress in psychiatry. Freud's book *The Interpretation of Dreams* (1958) led to the development of psychoanalysis, which was applied to the treatment of insomnia.

Psychoactive medications became widely used with the introduction of the phenothiazines in the 1950s, but hypnotic medications, particularly the barbiturates, had been in common usage since barbital was introduced in 1903. The 1960s saw the introduction of the benzodiazepine hypnotics, which largely replaced the barbiturates in the late 1970s. However, the 1980s saw a decline in the use of hypnotics with increased physician and public awareness of the disadvantages of chronic hypnotic use. Insomnia became recognized as a symptom rather than a diagnosis, and treatment was directed to the underlying physical or psychological causes.

Several books on sleep had a major influence on the development of sleep disorders medicine. Pieron's *Le problème physiologique du sommeil* in 1913 summarized the scientific sleep literature at that time. A similar approach was taken by Kleitman, who produced his monumental treatise, *Sleep and Wakefulness*, in 1939 (updated in 1963 to contain 4337 references) (Kleitman, 1963). The Association of Sleep Disorder Centers classification committee, chaired by Howard Roffwarg, produced the *Diagnostic Classification of Sleep and Arousal Disorders* in 1979; it ushered in the modern era of sleep diagnoses and became the first classification to be widely used. *The Principles and Practice of Sleep Disorders Medicine,* edited by Meir Kryger, Thomas Roth, and William Dement in 1989, was the first comprehensive textbook on basic sleep research and clinical sleep medicine (Kryger et al., 1989).

Increased knowledge about sleep and sleep disorders in general has resulted from the research of a few core sleep disorders, which include narcolepsy, obstructive sleep apnea syndrome, and the insomnias.

Following Gélineau's description in the late 19th century, narcolepsy was brought to general recognition in 1926 by the Australian-born neurologist William John Adie (1886–1935) (Adie, 1926), and stimulants were first used for treatment by Otakar Janota (1898–1969) and A. Skala in 1930. In 1941 John Burton Dynes and Knox H. Finley applied the electroencephalograph to the diagnosis of narcolepsy (Dynes and Finley, 1941), and the characteristic sleep-onset REM period of night sleep was discovered in 1960 by Gerald Vogel. Dement and colleagues at Stanford University developed a narcoleptic dog colony in the 1970s, which advanced the understanding of the biochemical and neuroanatomical bases of the disorder. The Multiple Sleep Latency Test was applied to the diagnosis by Richardson et al. in 1978, and the documentation of a strong association between the histocompatability antigen HLA-DR2 and narcolepsy was made by Yutaka Honda and colleagues in 1984 (Juji et al., 1984).

Following the reports of snoring, sleepiness, and obesity in the 19th century, Sir William Osler (1849–1919) referred in 1906 to Dickens' description of Joe (Osler, 1906): "An extraordinary phenomenon in excessively fat young persons is an uncontrollable tendency to sleep – like the fat boy in *Pickwick*."

Charles Sidney Burwell in 1956 brought general recognition to obstructive sleep apnea syndrome, which he called the "pickwickian syndrome" (Burwell et al., 1956), and the first objective documentation of polysomnographic features was simultaneously reported by Henri Gastaut and Jung in 1965 (Gastaut et al., 1965; Jung and Kuhlo, 1965). Although the tracheotomy had been performed since the time of Asclepiades (first century BC), Wolfgang Kuhlo and Erich Doll in 1972 reported that it provided an effective treatment of the obstructive sleep apnea syndrome. Tanenosuke Ikematsu in 1964 popularized uvulopalatopharyngoplasty surgery for the treatment of snoring, which was subsequently applied to the obstructive sleep apnea syndrome by Shiro Fujita in 1981 (Fujita et al., 1981). The same year, nasal continuous positive airway pressure treatment was described by Colin Sullivan and subsequently became the treatment of choice (Sullivan et al., 1981).

Another sleep-related breathing disorder called "Ondine's curse" was first reported by John W. Severinghaus and Robert A. Mitchell in 1962. Named after the water nymph in Jean Giraudoux's play *Ondine* (1954), this disorder was characterized by the failure of automatic ventilation that could lead to fatal apnea during sleep:

> *Live! It's easy to say. If at least I could work up a little interest in living – but I'm too tired to make the effort. Since you left me, Ondine, all the things my body once did by itself, it now only does by special order... I have to supervise five senses, two hundred bones, a thousand muscles. A single moment of inattention, and I forget to breathe. He died, they will say, because it was a nuisance to breathe (Giraudoux, 1954, Act III).*

Insomnia received more interest in earlier centuries than in the first half of the 20th century, probably because of the availability of effective hypnotic medications. Frederick Snyder in the 1960s recognized and promoted the importance of psychiatric disorders in sleep medicine, especially depression: "Troubled minds have troubled sleep, and troubled sleep causes troubled minds" (Snyder, 1969).

The polysomnograph was applied to the investigation of patients with insomnia following the discovery of obstructive sleep apnea in 1965, and objective measures of hypnotic effectiveness were developed by Kales et al. in 1969. The concept of a conditioned insomnia (psychophysiological insomnia) was first presented in the *Diagnostic Classification of Sleep and Arousal Disorders* (Association of Sleep Disorder Centers, 1979), and subsequently became recognized as a common form of primary insomnia. The behavioral technique "stimulus control" developed by Richard Bootzin in 1972 was an effective treatment of insomnia, as was "sleep restriction therapy," developed by Arthur Spielman in 1987 (Spielman et al., 1987).

Circadian rhythm sleep disorders were recognized in the late 1970s, partly due to recognition of the chronobiological features of "jet lag" and "shift work." Thomas A. Edison, who was responsible for the development of the electric light bulb, which stimulated the development of shift work, had his own views on sleep:

> *In my opinion sleep is a habit, acquired by the environment. Like all habits it is generally carried to extremes. The man that sleeps four hours soundly is better off than a dreamy sleeper of eight hours (Baldwin, 1995).*

The atypical, sleep-onset insomnia called the "delayed sleep phase syndrome," discovered by Weitzman and colleagues in 1981, led to a radically different form of treatment called "chronotherapy," which was based on chronobiological principles (Czeisler et al., 1981; Weitzman et al., 1981).

Many other sleep disorders have been discovered in the 20th century, including REM sleep behavior disorder by Carlos Schenck et al. in 1986; paroxysmal nocturnal dystonia in 1981 by Lugaresi & Cirignotta and fatal familial insomnia in 1986 by Lugaresi et al.; and food allergy insomnia by Andre Kahn et al. in 1985.

General and medical awareness of sleep disorders has dramatically increased since the 1970s through the contributions of sleep disorders clinicians and the sleep societies. In addition to those mentioned, a few of the many who have contributed to this recognition include: Roger Broughton, Michel Billiard, Christian Guilleminault, Peter Hauri, J. David Parkes, the late Pierre Passouant, and Bedrich Roth.

Sleep disorders medicine

> *we have created a new clinical specialty, sleep disorders medicine! whose task is to watch over all of us while we are asleep (William Dement 1985).*

Organized sleep disorders medicine in the USA began with the founding of the Association for the

Psychophysiological Study of Sleep in 1961, an association comprised of sleep researchers, many with clinical interests. Sleep research led to the investigation of sleep disorders, which resulted in the establishment in the early 1970s of clinical sleep disorder centers for the diagnosis and treatment of patients. In 1976, the Association of Sleep Disorder Centers (ASDC) was founded. The first sleep disorder center to be engaged in active patient evaluations and treatment was that established at Stanford University in California by Dement. An accreditation process for sleep disorders centers was established by the ASDC, and the first to be accredited in 1977 was the Sleep–Wake Disorders Unit, headed by Weitzman, at Montefiore Medical Center in New York.

In 1978, the Association of Polysomnographic Technologists, founded by Peter Anderson McGregor, set standards of practice for polysomnographic technologists. In 2007 the association changed its name to the American Association of Sleep Technologists.

In 1983 the Association for the Psychophysiology Study of Sleep was renamed the Sleep Research Society and in 1984 the Clinical Sleep Society was founded as the membership branch of the Association of Sleep Disorder Centers. In 1986, the Association of Sleep Disorder Centers, the Clinical Sleep Society, the Sleep Research Society, and the Association of Polysomnographic Technologists formed a federation called the Association of Professional Sleep Societies. The Association of Sleep Disorder Centers was renamed as the American Sleep Disorders Association in 1987. Subsequently the name was again changed in 1999 to the American Academy of Sleep Medicine.

In 1978, the medical journal *Sleep* was created to present research and clinical articles on sleep, and in 1979 a complete issue was devoted to the diagnostic classification of sleep and arousal disorders (Association of Sleep Disorder Centers, 1979). The *International Classification of Sleep Disorders* manual was produced in 1990 and a second edition was produced in 1997 (American Sleep Disorders Association, 1990, 1997). Several other sleep journals were created, including *Sleep Medicine Reviews* (1997), *Sleep Medicine* (2000), *Behavioral Sleep Medicine* (2003), and the *Clinical Journal of Sleep Medicine* (2005), the official journal of the American Academy of Sleep Medicine.

Clinicians who were trained in sleep medicine were eligible to take a certification examination that was first held in 1978. The examination was open to both physicians and other doctoral clinicians. With the recognition of the importance of behavioral treatments in sleep medicine, especially in insomnia, a board examination was developed in 2003 for clinicians, mainly psychologists but also physicians, in behavioral sleep medicine.

In 2005, a fellowship training program was approved by the American College of Graduate Medical Education for eligibility to take a board certification examination in sleep medicine. The first examination was held in 2007. This examination of the Board on Internal Medicine is open to physicians who have been board-certified by one of the specialty boards of the American Board of Psychiatry and Neurology, the Board of Internal Medicine, the American Board of Pediatrics, or the American Board of Otolaryngology, and who have completed 1 year of sleep medicine fellowship training. Until 2011 physicians trained in sleep medicine who meet certain criteria of training are eligible to sit the Board of Sleep Medicine examination despite not having completed 1 year of American College of Graduate Medical Education-certified training.

A sleep-related foundation, the National Sleep Foundation, was created in 1990 by the American Sleep Disorders Association, and subsequently became independent of the association. The National Sleep Foundation is an independent nonprofit organization dedicated to improving public health and safety by achieving understanding of sleep and sleep disorders, and by supporting sleep-related education, research, and advocacy. The National Sleep Foundation relies on voluntary contributions, including grants from foundations, corporations, government agencies, and other organizations to support its programs. Another foundation, the American Sleep Medicine Foundation (formerly the Sleep Medicine Education and Research Foundation) was established by the American Academy of Sleep Medicine Board of Directors in March 1998 to promote education and fund research.

With the increased recognition of the importance of sleep disorders medicine many international sleep societies have been founded, beginning with the European Sleep Research Society in 1971, the Japanese Society for Sleep Research in 1978, the Belgian Association for the Study of Sleep in 1982, the Scandinavian Sleep Research Society in 1985, the Latin American Sleep Society in 1986, the Sleep Society of Canada in 1986, and the British Sleep Society in 1989. Sleep medicine has become a major branch of medicine with practitioners in nearly every country of the world.

The woods are lovely, dark, and deep,
But I have promises to keep,
And miles to go before I sleep,
And miles to go before I sleep.
(Robert Frost, 1923).

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