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HISTORICAL REVIEW

Who was the first to use the term Pickwickian in connection with sleepy patients? History of sleep apnoea syndrome

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Summary The symptoms and characteristics of sleep apnoea syndrome—excessive daytime sleepiness, loud snoring, restless and non-restorative sleep—are so impressive that it is difficult to understand why its recognition was delayed until the 1970s. The Centennial book of the American Thoracic Society credited Sidney Burwell for the discovery of Obstructive Sleep Apnoea Syndrome. This is only one of the many mistakes and misattributions regarding the history of sleep apnoea syndrome. The earliest descriptions of patients who presumably suffered from sleep apnoea were made in the 19th century. The term ''Pickwickian'' in connection with sleepy patients was introduced in 1889. The first electrophysiological sleep recordings of Pickwickian patients and the understanding of the syndrome as disordered breathing in sleep, were made during the late 1950s and 1960s. Its recognition as a public health problem was facilitated by Young et al.'s [Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-aged adulte. *N Engl J Med* 1993;**328**:1230–5] seminal paper documenting the prevalence of the syndrome in the general population, and by the accumulated evidence that the syndrome is a major cardiovascular risk factor. Bibliometric analysis of the literature on sleep apnoea reveals that future research will focus on the long-term outcomes of the syndrome, on the effects of treatment, and on the underlying mechanisms linking it with cardiovascular morbidity.

The first Pickwickian

In 2004, the American Thoracic Society celebrated its centennial anniversary. The book ''*Colleagues in Discovery: one hundred years of improving respiratory health*'' was published by the Society to commemorate this event.[1] In this book, for the year 1956 we find the following: ''Charles Sidney Burwell recognizes **Obstructive Sleep Apnoea** Syndrome (emphasis in origin) which he names ''Pickwickian syndrome'' after a character in Dickens's *The Pickwick papers*. Burwell's

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description leads to an explosion of research about, and new treatments of, the syndrome.'' Although the American Thoracic Society book is not the only one to mistakenly attribute the roots of sleep apnoea syndrome to Burwell et al.'s[2] paper: *Extreme Obesity Associated with Alveolar Hypoventilation—A Pickwickian Syndrome*, published in November 1956 in the American Journal of Medicine, their mistake is no doubt the most noteworthy and misleading one. It can be categorically stated that Burwell et al. did not recognize obstructive sleep apnoea syndrome and, more so, were not the first to use the term Pickwickian in connection with sleepy patients.

Burwell et al. described a case of a sleepy, obese patient as follows:

> He was a fifty-one year old business executive who entered the hospital because of obesity, fatigue and somnolence. This patient reported that he had been overweight all his remembered life and for many years had weighed approximately 100 kg. When this weight was maintained, he was alert, vigorous and able to work long hours... As the patient gained weight his symptoms appeared and became worse... He had often fallen asleep while carrying on his daily routine... Finally an experience which indicated the severity of his disability led him to seek hospital care. The patient was accustomed to playing poker once a week and on this crucial occasion he was dealt a hand of three aces and two kings. This hand is called a ''full house''. *Because he had dropped off to sleep he failed to take advantage of this opportunity.* A few days later he entered the Peter Bent Brigham Hospital. (Emphasis in the original)

Although it can be assumed from the case description with a great degree of certainty that the card player indeed suffered from obstructive sleep apnoea syndrome, Burwell and his colleagues described their patient's sleep in the following way:

> Irregular twitching movements of many muscle groups were observed while the patient was sleeping and during the more active hours. His respirations were variable but generally were shallow and rapid and exhibited a definite tendency to periodicity.

Even though they noticed the periodicity in breathing was somewhat unusual:

> This periodic respiration differed from the usual Cheyne–Stokes breathing in that periods of apnea alternated with periods of tachypnea rather than hyperpnea.

they came to the erroneous conclusion that it was caused by inadequate alveolar ventilation that caused this patient's chronic hypoxia, and chronic hypercapnia. These in turn could produce cyanosis and the resultant polycythemia, somnolence, periodic breathing and the other symptoms and signs present in this patient.

Sieker et al.[3] described a similar case a year before Burwell et al., and even provided an identical explanation for the patient's sleepiness, but Sieker et al.'s case had never gained the attention commanded by Burwell's card player that was cited more than 550 times in the medical literature.

The resemblance between the sleepy and plump patients and Dickens's character Joe, was made by sharp eye practitioners more than 50 years before Burwell et al. described their sleepy poker player. Richard Caton (1842–1926) from Liverpool England, better known for being the first to record electrical currents from an exposed animal brain, presented to the clinical society of London a case he erroneously termed ''A case of Narcolepsy'' in 1889[4]:

> The patient, S., age 37, a poulterer, was admitted into my wards in Liverpool Royal Infirmary on January 12, 1888, complaining of intense drowsiness and chronic psoriasis. (p. 133).

His medical history was uneventful except for a recent gain of weight:

> At the beginning of 1881 his weight was 11 st. 4 lbs. (~71 kg), during that year he gained 4 st. in weight (~25 kg), and coincidently a tendency to drowsiness showed itself, and progressively increased month after month, causing him great inconvenience. He had been fond of attending the theatre, but now he slept soundly through the most exciting drama. During the year 1882 he further gained 3 st. in weight; the tendency to sleep became constant and overpowering. It had been his habit to entertain guests frequently, but now he fell soundly asleep while carving the joint at his own table. Reading and writing became quite impossible; the moment he sat down in a chair sleep came on, and even when standing or walking he would sink into sleep. Constantly while serving customers in his shop, sleep would come on as he stood by the counter; he would waken and find himself holding in his hand the duck or chicken which he had been selling to a customer a quarter an

> hour before, the customer having meantime departed.

The unusual features of sleep in Caton's case leaves no doubts as to the nature of his disorder:

> When in sound asleep a very peculiar state of the glottis is observed, a spasmodic closure entirely suspending respiration. The thorax and abdomen are seen to heave from fruitless contractions of inspiratory and expiratory muscles; their efforts increase in violence for about a minute or a minute and a half, the skin meantime becoming more and more cyanosed, until at last, when the condition to the onlooker is most alarming, the glottic obstruction yields, a series of long inspirations and expirations follows, and the cyanosis disappears. This acute dyspnoeic attack does not awaken the patient. ...If in the midst of the dyspnoeic attack he be forcibly aroused, the glottic spasm at once relaxes.

Caton went on and said that:

> The night nurse states that these attacks go on all through the night. Patient is himself unaware of them, excepting from what others tell him. His wife states that they have occurred with varying frequency for some years.

He concluded his presentation by admitting that:

> I have not yet found anything in medical literature which throws much light on this case, and as the patient is likely to come into my hands again, I shall be very grateful if any member of this Society can give me hints in reference to diagnosis or treatment.

Although the members of the society did not provide Caton with helpful hints regarding the nature of his case, Christopher Heath, the president of the society, alluded to the resemblance between Caton's case and Joe, the sleepy character in Dickens's book *The Posthumous papers of the Pickwick club* originally published in 1837.[5]

A sleepy card player, who apparently suffered from sleep apnoea, was also described in the medical literature many years before Burwell et al's publication. In 1889, Morison described a sleepy patient in a paper entitled "Somnolence with cyanosis cured by massage" in the following words:

> S.G. aged 43 years, a diamond merchant, tall, stout, married, and a father of healthy family....suffered for at least fifteen years from drowsiness, and during the last two years became deeply somnolent. He would fall asleep while interested in and playing a game of cards, the cards suddenly dropping out of his hands on to the table, and he beginning to snore, and his face becoming darkly engorged until his companions succeeded in rousing him (p. 277). [6]

Like Joe, the Pickwickian character, once he fell asleep while standing on a door-step waiting for the door to be opened. The description of his sleep suggests that he suffered from sleep apnoea:

> I have myself observed him asleep in bed with an intensely cyanotic countenance, a condition from which he was aroused after a snorting and choking sound issued from his respiratory passages, the cyanosis then gradually disappearing. (p 278).

Interestingly, Morison was aware of Caton's case, but did not agree with the term "narcolepsy" used by Caton to describe his case. He treated his patients with vigorous massage for 5 weeks, which resulted in a loss of 15 lbs and dramatic improvement in his sleepiness. Thus, "on January 9, he went to a party and stayed till 3 AM and felt no drowsiness in spite of his having taken a glass of champagne."

More on the pre-20th century literature on sleepy patients and respiratory impairments in sleep and on other sharp eye physicians who noticed the resemblance between sleepy patients and Joe, the Pickwickian boy, can be found elsewhere.[7–9]

The first polysomnographic recording

Berger, a psychiatrist from Jena, Germany, recorded the first human electroencephalograms (EEGs) in 1924. Berger's paper *Über das Elektrenkephalogramm des Menschen* (On the EEG in humans) was published in 1929 in the *Archive für Psychiatrie und Nervenkrankheiten*.[10] Later, Alfred Loomis in the mid-1930s, showed that in humans EEG patterns changed dramatically during a night's sleep.[11] In light of the relatively recent history of electrophysiological monitoring during sleep it could be assumed that there will be no dispute about who made the first recordings in sleep apnoea patients. But this is not the case. In 1977, the Journal Respiration published a special supplemental issue entitled: "30 years—sleep apnoea," in which the leading paper, written by Wolfgang Kuhl,[a] was entitled: "History of clinical research on the sleep apnoea syndrome".[12] In this paper, Kuhl gave credit to Berger, Caton, Burwell et al., and Loomis et al., in addition to five papers of his own

[a]Early publications of Kuhl were published under the name Wolfgang Kuhlo.

as pioneers in the field of electrophysiological investigation of sleep and sleep apnoea, but neglected to cite the two first publications.

Sleep recordings in Pickwickian patients

The first physiological recordings in sleeping Pickwickian patients were conducted in 1959 at the Ludolf Krehl Klinik of the Heidelberg University Hospital, and a year later at the National Institutes of Health (NIH), at Bethesda in the United States. The significance of these observations remained completely unnoticed by all who came later and their primacy has so far gained almost no recognition.

Werner Gerardy completed his medical studies at the University of Mainz, Germany, in 1951. Two years later, he received an appointment to the internal medicine department at the Heidelberg University Hospital. The research interest in the department focused on the effects of metabolic diseases on electroencephalographic activity. As some of these diseases were also characterized by alteration in autonomic nervous system activity, the hospital technicians made a number of adjustments to the electroencephalograph machine for Gerardy so that it would be able to record breathing and pulse rates at the same time as it recorded brain waves. It was pure chance that led him to conduct a sleep recording, the first in medical history, on a Pickwickian patient. Gerardy was assigned to make an EEG monitoring of a Pickwickian patient hospitalized because of reduced work capacity and frequent headaches upon waking, who fainted and nearly died in his sleep. In their article published in German in 1960, Gerardy et al.[13] describe the sleep of this patient as follows:

> Approximately ten minutes after the commencement of recording, the patient was sleeping deeply. Here, periodic breathing was observed with short suspensions with the tongue sometimes falling back at the onset of each suspension so that there was no air flow, despite the increased movements of the thorax. Then the patient woke up suddenly, the tongue moved forward and a second, or a second and a half later, the first breath appeared. The heart rate during the suspension of breathing became slower and slower, but was greatly accelerated with renewal of breathing. (translated from German)

Following the recordings of this patient, Gerardy and his colleagues examined another Pickwickian patient, and with him, too, they observed the same phenomenon. Both patients, who were employed as clerks by the postal authority, suffered from obesity and a tendency to fall asleep ''under any conditions and at any time''. Both showed a great improvement in their sleep and daytime alertness after losing weight.

Gerardy et al.'s paper was the first report in the medical literature on apnoeic events in Pickwickian patients. The explanation given by Gerardy and his colleagues for the suspension of breathing during sleep was no different from the views prevailing at the time regarding the causes of breathing disorders and drowsiness in Pickwickian patients—''carbon dioxide poisoning''. Disappointingly, Gerardy and his colleagues did not ascribe importance to the fact that at the onset of an apnoea, the Pickwickian patient's tongue fell backwards, blocking the pharynx, and that the renewal of breathing was accompanied by a forward movement of the tongue. They viewed this purely as a sign of deepening sleep.

Awakenings or falling asleep?

A year after Gerardy et al.'s article was published in Germany, Drachman and Gumnit of the NHI published their article entitled *Periodic Alteration of Consciousness in the Pickwickian Syndrome* in the Achieves of Neurology.[14] Gumnit, a researcher in the neurophysiology and electroencephalography laboratories at NIH, had a great interest in EEG of epileptic patients and patients who had sustained head trauma but also showed interest in the tendency of Pickwickian patients to frequently fall asleep and awaken during the day. Together with Drachman he investigated a drowsy, 57-year-old female, Pickwickian patient, hospitalized on March 13, 1961 because of an uncontrollable tendency to fall asleep during the day that had gone on for several years. She was an ice-cream vendor whose enthusiasm for sampling her wares had cost her a weight increase of 20 kg in a short period of 3 months. Drachman and Gumnit noted that despite her falling asleep numerous times during the day and her falling asleep immediately at night, her sleep was restless. Moreover, people who observed her asleep testified that she tended to choke and suffocate as she slept.

Like Gerardy and his colleagues, Drachman and Gumnit made the recordings during the day. They observed that the moment the patient's EEG showed signs of sleep, her breathing ceased and arterial oxygen saturation level dropped to a minimum of almost 50%. And then, about half a minute later, the patient awakened again, started

breathing and the oxygen saturation level rose, only for the patient to stop breathing again after a few seconds, and so on and so forth. Drachman and Gumnit concluded that she fell asleep approximately 200 times, for short periods of about half a minute each time! We know today that the patient's true condition was exactly the opposite: she did not, in fact, *fall* asleep 200 times but *awakened* from sleep 200 times! Interestingly, Drachman and Gumnit cited Gerardy et al.'s article, and like them, explained the Pickwickian patients' excessive sleepiness as carbon dioxide ''poisoning.'' Not surprisingly, a strict diet of 600 calories per day for 6 days helped the ice-cream loving patient to shed 20 kg and resulted in almost complete disappearance of her daytime sleepiness.

The Ski resort symposium

Kuhl, who studied medicine in Freiburg and specialized in neurology, had a great interest in EEG changes that accompany the process of falling asleep. In 1960, he was appointed Director of the EEG laboratory at the Freiburg University Department of Neurophysiology, which was headed by Richard Jung, one of the pioneers of neurophysiology in Germany, who had a great interest in the Pickwickian syndrome. Jung, who had been very impressed by the work of Bulow and Ingvar[15] on breathing instability during the falling-asleep process, suggested to Kuhl that he conduct nighttime sleep recordings on Pickwickian patients. He assumed that in these patients the breathing instability would continue throughout the night. Kuhl's recordings indeed showed that the moment Pickwickian patients fell asleep they stopped breathing and immediately awakened and renewed their breathing, only to fall asleep again and stop breathing. But in contrast to their predecessors who did not connect the sleep disorder with daytime sleepiness, Kuhl and Jung correctly concluded that excessive daytime sleepiness in Pickwickian patients is explained by their sleep fragmentation, and not because of carbon dioxide poisoning. Kuhl presented their findings at the skiing conference held at Oberstdorf in the German Alps in 1964. In Kuhl's audience were two people who immediately grasped the great importance and clinical significance of his findings: Henri Gastaut from Marseilles, and his former student, Elio Lugaresi from Bologna. Immediately after the meeting, Gastaut, a world-renowned neurologist who headed the Neurobiological Research Unit in Marseilles, assigned two of his younger colleagues, Duron and Tassinari, to monitor Pickwickian patients' sleep. They not only confirmed Kuhl and Jung findings, but also expanded them. Using measurements of mouth and nostril airflow in addition to chest movements, they demonstrated that the reason for the apnoeic events during sleep was in the blockage of the upper airways during sleep in spite of continuous respiratory effort.[16,17] Therefore, while Kuhl and Jung ascribed the disorder to a disruption of respiratory centre activity during sleep, Gastaut and his colleagues attributed it to a blockage of the airways.

Jung and Kuhl published their first article (in English) on breathing disorders in sleep of Pickwickian patients in a proceedings of an international symposium held at the University of Zurich in September 1964, dedicated to neurophysiology of sleep.[18] In it, they described sleep recordings of three Pickwickian patients. Interestingly, in each of the three patients a weight reduction of 10–20 kg brought about a significant improvement in breathing during sleep and daytime sleepiness, albeit the apnoeas did not disappear completely. It is interesting to note that Kuhl and Jung cited the articles by Gerardy et al. and Drachman and Gumnit, but did not mention their particular findings at all.

It is hard to say whether Kuhl and Jung's paper left any impression on the participants in the Zurich symposium. F. Hoff of Frankfort, who summed up the symposium from the internist's point of view, did not mention their findings, and neither did Giuseppe Moruzzi, one of the greatest neurophysiologists of the time, who summed up the symposium from the neurophysiologist's standpoint.

Contributions of the Bologna group

Elio Lugaresi and G. Coccagna from Bologna, also attended Kuhl's lecture at Oberstdorf. They, too, were not newcomers to the field of sleep research and immediately grasped the importance of Kuhl's observations. Lugaresi set up a sleep research laboratory in Bologna where they made the first sleep recordings in patients with ''nervous legs syndrome''.[19] The Bologna group's findings in Pickwickian patients supported those of Gastaut et al. and documented three types of apnoea: obstructive central and mixed. Shortly thereafter, Daniel Kurtz and his colleagues of Strasbourg added the hypopnoea, or partial apnoea, that like apnoeas ends with a brief awakening and a slight drop in the oxygen saturation level. Lugaresi and his colleagues made another seminal discovery in Pickwickian patients. With the help of Paola Verucci Coccagna, an anaesthetist with a wide experience

in monitoring vital signs of anesthetized patients, they documented extreme variations in both systemic and pulmonary blood pressures during sleep in Pickwickian patients.[20] The blood pressures dropped at the onset of the apnoea and rose dramatically when breathing was resumed, coincidentally with the brief awakening from sleep.

Lugaresi et al.'s observations on the apnoea-related dramatic rise in blood pressure clearly showed that the occurrence of apnoea during sleep was not simply a strange medical episode but a disorder that called for treatment, and even aggressive treatment. Up to that time, a reduction in weight was the only treatment for Pickwickian patients, but losing weight was no simple thing for such obese patients and only a few were capable of losing weight and persevering for an extended period. A chance observation by Kuhl led to the introduction of a new radical way to treat apnoeas during sleep by means of bypassing the obstruction by tracheostomy. One of Kuhl's Pickwickian patients had sunk into a protracted coma as a result of what was diagnosed as severe carbon dioxide poisoning. To save him from this grave situation a tracheostomy was performed. To their astonishment, the patient awakened from his coma immediately after the procedure and appeared to have made a complete recovery not only from his sleep breathing disorders, but also from his attacks of daytime sleepiness.[21] This case convinced Kuhl that Gastaut and Lugaresi were right, and that the cause of apnoeas in sleep is upper airway obstruction rather than a disruption in the activity of the respiratory centre. On hearing about Kuhl's case, Lugaresi and his colleagues managed to convince the staff of the Bologna surgical department to perform tracheostomy on the Pickwickian patients in their care. Within a very short time, six patients underwent the procedure and on the first night after surgery, all of them showed that the apnoeas had completely disappeared, together with the daytime sleepiness.[22] Furthermore, post-treatment systemic and pulmonary blood pressure recordings showed a significant improvement while pathological signs in two patients disappeared from their sleep electrocardiogram recordings.

Convinced of the importance of their new findings in Pickwickian patients, Lugaresi and Coccagna decided to organize a "Sleep Disorders" conference in Bologna. The conference, held in 1967 was the first of a series on this subject to be organized by the Bologna group, and drew sleep researchers from all over the world. It was attended by Dement and Rechtschaffen, the pioneering leaders of modern sleep research in the United States, Gastaut and Passouant from France, Oswald from Scotland, Roth from Prague, and Hishikawa from Japan. From the perspective of 40 years, it can be stated that the Bologna conference laid the cornerstone for "sleep medicine", and all its participants would, over the years, become key figures in the study of sleep and its disorders. Yet it was disappointing to see that the reports of Lugaresi and his colleagues on their findings in Pickwickian patients left no impression at all on the congress participants, and not one of them rushed back to his laboratory to study sleep breathing disorders. The programme of the first scientific conferences of the European Sleep Research Society that was founded in 1965, does not reveal any presentations on the Pickwickian syndrome, except for two further case studies. Brief reports on sleep recordings conducted on the odd Pickwickian patient appeared here and there in the medical literature, but they contained no innovations. In Prague, for example, sleep recordings were conducted on a small number of Pickwickian patients who were referred for testing by an obesity clinic.[23]

Few years later, the Bologna group organized another scientific conference that was devoted entirely to the subject of sleep breathing disorders. At the conference, that was held at the Italian resort of Rimini, papers were presented on sleep breathing disorders, sleep recordings of the patients in question, and treatment using tracheostomy. The papers were published in a special edition of *Bulletin de Physiopathologie Respiratoire*. This was the first time an attempt was made to distinguish between the different types of the Pickwickian patients. Caroll from Baltimore specified no fewer than 10 different types of Pickwickian Syndromes.[24] One of them, which he termed the Gastaut's type, was characterized by "obesity with hypersomnia secondary to sleep loss, secondary to upper airway obstruction." Later, he reduced the number of types to two, with and without hypersomnia.

Waking up to breathing in sleep in the US

Except for the single article by Gumnit and Drachman on the ice-cream loving Pickwickian patient, very little was done in the US on sleep disordered breathing until the mid-1970s. The first sleep clinic in the US was opened by Dement at Stanford in 1970. But the first patients seen at the newly opened sleep clinic were insomniacs and narcoleptics. As Dement revealed in his book *Some Must Watch While Some Must Sleep*,[25] the first two Pickwickian patients were examined in Stanford in 1969, but the findings neither aroused any great

excitement nor generated a publication. The first presentation on breathing in sleep from the Stanford group was made by Guilleminault, who joined the Stanford sleep clinic in 1972, in the Annual Meeting of the APSS that took place in Jackson Hole, Wyoming. But the sleep community was still not ready to hear about it, and his lecture did not arouse much response. The major contributions of the Stanford group came few years later when they demonstrated that insomnia associated with upper airway obstruction during sleep can occur in people with normal weight,[26] and that a relatively large number of patients referred to the Stanford sleep clinic because of sleep complaints had sleep disordered breathing.[27] In that paper they used the term "Sleep Apnoea Syndrome" for the first time and provided a definition for the syndrome that was based on the polysomnographic findings. Sleep apnoea syndrome as defined by Guilleminault and Dement occurs when at least 30 apnoeas of minimum duration of 10 s each are detected during sleep. Later, this definition was modified to take into account the individual variations in sleep duration. This study had two additional noteworthy observations, first that the 35 patients with sleep apnoea syndrome comprised 34 men and a single woman, and second, that almost half of the patients with sleep apnoea suffered from hypertension. In years to come the association between sleep apnoea syndrome and the cardiovascular system would become the driving force behind sleep medicine.

Sleep apnoea in the last 40 years

The burst of publications on sleep in Pickwickian patients in the early 1970s did not have much impact on medical practice even though some of the early publications were widely cited. Gastaut et al.'s[17] Brain Research paper, for example, was cited 228 times and Coccagna et al.'s[20] paper on systemic and pulmonary surges in blood pressure during sleep in Pickwickian patients was cited 193 times. But, as explained to me by Elio Lugaressi, papers that were not published in the leading medical journals such as The New England Journal of Medicine, Lancet, or the British Medical Journal, had little chance to affect the everyday practice of medicine.

Analysis of what happened since the early seventies is a relatively easy task as the accessibility to large bibliometric databases have undergone an enormous change in recent years. Twenty years ago, searching for pre-20th century sleep-related medical publications required the tedious manual search of the US Index-Catalogue of the Library of the Surgeon General's Office. Once identifying the relevant publications, they have to be located in rare books departments that exist in only few privileged libraries. Today, with the advent of computers and internet, access to bibliometric databases are done with lightening speed, which make the analysis of the trend and development of publications in any medical field easier than ever. The present analyses of the developments in sleep apnoea research in the last 40 years is based on the ISI Web of Science database that is available for medicine and life sciences from 1965 (http://portal.isiknowledge.com). Of note, other databases may be different from that of the ISI with respect to the scope and number of journals covered, the definitions of documents, or in the specific features of their search engines.

Using the word "sleep" if appearing in either the title, abstract, or as a key word of a paper, reveals a total of 66,343 publications during the period from 1965 to December 31, 2006. Of these 43,979 (66.3%) are research articles, 3622 (5.4%) reviews, 1938 (2.9%) editorials, 1981 (3%) letters to the editor, and 14,832 (21.8%) meeting abstracts or other types of documents. The following analyses were all performed on research articles only. Figure 1 presents the annual numbers of research articles for the period 1965–2006. Two different periods—from 1965 to 1990 and from 1991 to 2006—can be seen. Linear regressions fitted to the two time periods revealed a dramatic change in the annual rate of sleep-related publications; they increased 5-fold from 20.4/year during 1965–1990 to 107.5/year during 1991–2006. The reason for the dramatic increase in the number of sleep-related publications during the early 1990s is unclear. This could represent a major increase in sleep research publications, or a technical improvement in the ISI

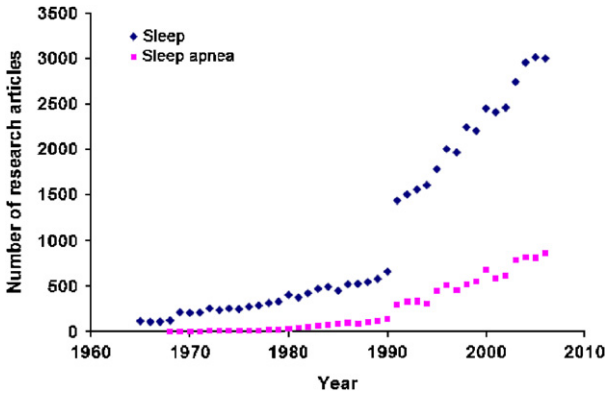

Figure 1 Annual numbers of "sleep" and "sleep apnoea"-related research articles published during 1965–2006 (data based on the ISI Web of Science).

search engines that allowed identification of a larger number of relevant papers.

A similar analysis was done for sleep apnoea-related publications with the following key words: "sleep apnea", "sleep apnoea", "sleep disordered breathing", "Pickwickian syndrome", "Upper airway occlusion during sleep," and "snoring," if appeared in the title, abstract, or key words. Publications in which any of these terms was mentioned indirectly were not taken into account. Overall, there were 15,064 sleep-apnoea-related publications during 1965–December 31, 2006 of which 9869 (65.6%) are research articles, 922 (6.1%) reviews, 610 (4.0%) editorials, 843 letters (5.6%), and 2807 (18.8%) meeting abstracts or other types of publications. The curve depicting the annual number of publications during this period is similar to that of all sleep-related publications with more than double the number of research articles from 1990 to 1991 (139–294). Similarly, there was more than 6-fold increase in the annual rate of publications from 6/year during 1965–1990 to 38.7/year during 1991–2006 (Figure 1).

One of the attractive features of the bibliometric databases is that it allows analyses based on user-defined criteria such as authors, institutes or countries at a press of a button. This provides new insights into the dynamics of the evolution of specific fields of science, to determine critical publications that have made important influences on the directions of research, and even allows to predict future trends and newly emerging directions of research. Several of these analyses will be presented now.

Contribution of countries: Figure 2 presents the total number of sleep apnoea-related research articles in different countries. Not surprisingly, the largest number of research articles has been published in the USA (40%), followed by Canada (8%), Germany (7%), United Kingdom (7%), France (7%), Japan (6%) and Australia (5%). This picture, however, changed once the number of publications is normalized to the size of the population in each country. After normalization, Israel leads with 0.354 papers/10,000 persons, followed by Sweden (0.336), Finland (0.316), Australia (0.252), Canada (0.238) and Switzerland (0.209). Similar results were found when normalization was made in reference to the gross national product of each country. Interestingly, Sweden, Switzerland and Israel top the list of nations as ranked by the total number of science and engineering publications per capita between 2000 and 2003.[28]

Contribution of authors: Four hundred and fifty-one authors have contributed more than 10 research articles on sleep apnoea-related subjects and 24 authors have contributed more than 50 research articles (Table 1). By far the most prolific is Christian Guilleminault from Stanford who authored 222 research articles, which is more than

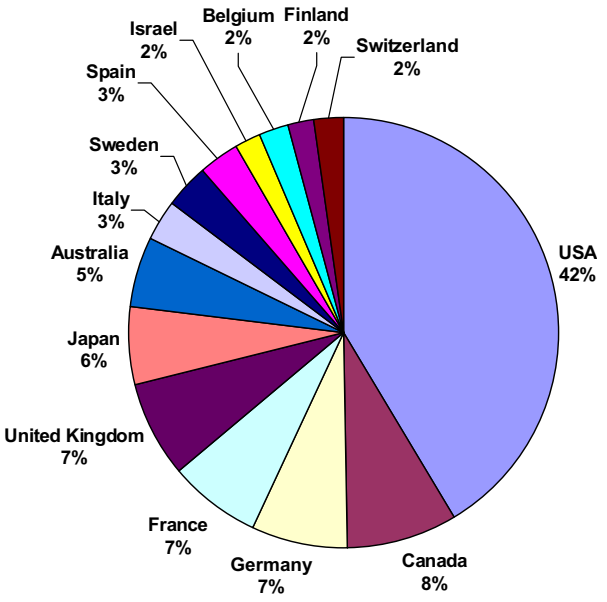

Figure 2 Percentages of "sleep apnoea"-related research articles published by researchers from different countries during 1965–2006 (data based on the ISI Web of Science).

Table 1 The 20 most prolific authors in the field of sleep apnoea research with at least 50 research articles (data based on the ISI Web of Science for the period 1965–2006).

	Author	Number of publications
1	Guilleminault C	222
2	Peter JH	102
3	Douglas NJ	102
4	Redline S	85
5	Smith DP	80
6	Gozal D	79
7	White DP	79
8	Sullivan CE	78
9	Series F	76
10	Bradley TD	73
11	Schwartz AR	71
12	Hoffstein V	69
13	Krieger J	69
14	Levy P	66
15	Pepin JL	64
16	Stradling JR	62
17	Lavie P	60
18	Penzel T	53
19	Hedner J	52
20	Pack AI	51

twice the number of publications of Herman Peter from the University of Marburg in Germany, and Neil Douglas from Edinburgh in Scotland ($n = 102$), who shared the second and third places on the list. The above analysis relied only on the number of publications disregarding their impact. The *h*-index was suggested as a measure for an impact of a researcher that reflects the balance between the number of publications and the number of citations per publication.[29] A scientist with an index of *h* has published *h* papers with at least *h* citations each. Applying this analysis to the list of the most prolific authors in the sleep apnoea field reveals a somewhat different picture. While Christian Guilleminault remains at the top of the list with *h* factor of 59, Susan Redline was in the second place ($h = 36$) and Neil Douglas and Douglas Bradely shared the third and fourth places ($h = 35$).

Top cited papers in sleep apnoea

Table 2 presents the 10 top cited papers in seep apnoea research. By far, the most cited paper is

Table 2 The 10 most cited research articles in the field of sleep apnoea (data based on the ISI Web of Science for 1965–2006).

- Young T, Palta M, Dempsey J et al.
  The occurrence of sleep-disordered breathing among middle-age adults
  New England Journal of Medicine 1993;**328**:1230–5
  Times cited: 1946
- Remmers JE, Degroot WJ, Sauerland EK et al.
  Pathogenesis of upper airway occlusion during sleep
  Journal of Applied Physiology 1978;**44**:931–38.
  Times cited: 1088
- Sullivan CE, Berthon-Jones M, Issa FG et al.
  Reversal of obstructive sleep-apnoea by continuous positive airway pressure applied through the nares.
  The Lancet 1981;**1**:862–5.
  Times cited: 954
- He J, Kryger MH, Zorick FJ et al.
  Mortality and apnoea index in obstructive sleep-apnoea—experience in 385 male patients
  Chest 1988;**94**:9–14
  Times cited: 747
- Peppard PE, Young T, Palta M et al.
  Prospective study of the association between sleep-disordered breathing and hypertension
  New England Journal of Medicine 2000;**342**:1378–84.
  Times cited: 569
- Block AJ, Boysen PG, Wynne JW et al.
  Sleep apnoea, hypopnea and oxygen desaturation in normal subjects—strong male predominance
  New England Journal of Medicine 1979;**300**:513–7.
  Times cited: 533
- Fujita S, Conway W, Zorick F et al.
  Surgical-correction of anatomic abnormalities in obstructive sleep-apnoea syndrome-uvulopalatopharyngoplasty
  Otolaryngology-Head and Neck Surgery 1981;**89**:923–34
  Times cited: 507
- Nieto FJ, Young TB, Lind BK et al.
  Association of sleep-disordered breathing, sleep apnoea, and hypertension in a large community-based study
  Journal of the American Medical Association 2000;**283**:1829–36
  Times cited: 472
- Guilleminault C, Stoohs R, Clerk A et al.
  A cause of excessive daytime sleepiness—the upper airway—resistance syndrome
  Chest 1993;**104**:781–7
  Times cited: 446
- Hung J, Whitford EG, Parsons RW et al.
  Association of sleep-apnoea with myocardial-infarction in men
  The Lancet 1990;**336**:261–4
  Times cited: 407

that of Young et al.[30] published in the New England Journal of Medicine that reported on the prevalence of sleep apnoea syndrome in the general population. Young et al. reported that 2% (women) and 4% (men) of the civil servants in the state of Wisconsin suffer from sleep apnoea syndrome defined as a polysomnographic finding of at least 5 apnoeas or hypopnoeas per hour of sleep and a complaint of excessive daytime sleepiness. Even though there were previous reports on the prevalence of sleep apnoea in the general population,[31–33] the quality of Young et al.'s research and their rigorous epidemiological methodology combined with the outstanding visibility of the New England Journal of Medicine, have made this paper the cornerstone of modern sleep medicine. Until December 31, 2006, Young et al.'s paper was cited 1986 times, which is almost twice the number of citations of the second most cited paper (Remmers et al.[34]; $N = 1090$,) published 10 years before Young et al's paper. In fact, the outstanding position of Young et al.'s paper is not limited to the field of sleep apnoea, it is the most cited paper of all 43,433 sleep-related research articles published since 1965. Young et al.'s paper was cited in 1529 research papers, 247 reviews, 114 editorials, and in 53 comments, letters and abstracts. Figure 3 depicts the annual number of the citations of Young et al. This shows a rapid increase in the number of citations from its publication in 1993 to a level of approximately 100 per year in 1996, followed by two more "jumps" from 100 to 150 citations/year in 1999, and from 150 to 200 citations/year in 2003. Noteworthy, Eliot Phillipson's editorial accompanying Young et al.'s paper: *Sleep-apnea a major public-health problem*[35] prophetically predicted the extraordinary influence of Young et al.'s paper.

Remaining top-cited sleep apnoea publications include Sullivan et al.'s[36] seminal paper in Lancet, "*Reversal of obstructive sleep-apnea by continuous positive airway pressure applied through the nares*" ($N = 954$), He et al.,[37] Chest's paper on mortality in patients with severe sleep apnoea ($N = 749$), Peppard et al.'s[38] paper in the New England Journal of Medicine that prospectively demonstrated significant association between hypertension and sleep apnoea ($N = 590$), Block et al.'s[39] New England Journal of Medicine's paper that documented the occurrence of apnoeas and its male predominance in normal subjects ($N = 533$); Fujita et al.'s[40] first description of the uvulo-palato-pharyngeal-plastic (UPPP) upper airway surgical procedure to treat sleep apnoea ($N = 510$), Nieto et al.'s[41] paper on the association between breathing disorders in sleep and hypertension in the population of the American Heart-Health Sleep study ($N = 486$), Guilleminault et al.'s[42] publication on the upper airway resistance syndrome ($N = 449$), and finally Hung et al.'s[43] paper on the association between sleep apnoea and myocardial infarction in men ($N = 412$).

Not surprisingly, 6 of the 10 top cited papers were published in the three journals having the highest impact factors (IF) among all medical journals—New England Journal of Medicine (IF = 44.01), Lancet (IF = 23.9) and JAMA (IF = 23.5). Four papers were published in specialized journals with considerably lower IF—Chest (IF = 4.0), Journal of Applied Physiology (IF = 3.0) and Otolaryngology-Head and Neck Surgery (IF = 1.2). Each of these papers, however, is one of the top 10 cited papers in each of the respective journals. This no doubt confirms Elio Lugaresi's acumen observation that only papers published in high profile journals have a chance to influence the everyday practice of medicine.

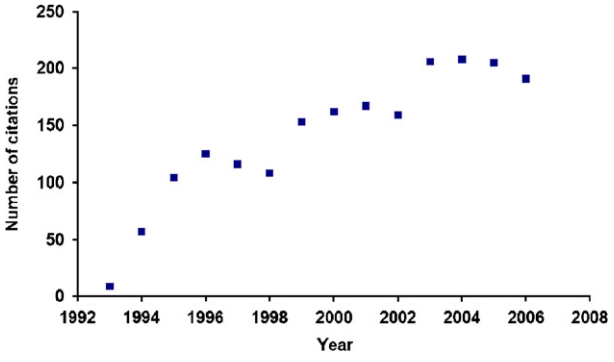

Figure 3 Annual number of citations of Young et al.'s[30] paper on the prevalence of sleep apnoea in the general population (data based on the ISI Web of Science).

Predicting the future

In addition to quantitative analysis of bibliometric data as demonstrated above, the ISI database allows an identification of future research trends by applying specific analytical techniques to measure associations between highly cited papers to form clusters, based on specified co-citation thresholds. Thus, a research front is a group of highly cited papers, referred to as *core papers*, in a specialized topic defined by cluster analysis. The clusters are named using a semi-automatic process based on frequently occurring words and phrases in the titles of the selected papers. The following research fronts were identified on 31 of December 2006.

Using the key words for sleep apnoea outlined above revealed 4 research fronts. The first front includes 6 papers that deal with the effect of nCPAP treatment on blood pressure[44–46] and on cardiovascular outcomes in patients with congestive heart failure.[47–49] The total number of citations for these papers is 668 times. Using randomized parallel groups or cross-over designs with a sham-CPAP as control, these papers demonstrated that effective nCPAP treatment reduced blood pressure in sleep apnoea patients and improved cardiac function in patients with congestive heart failure, particularly in patients with Cheyne Stokes breathing. However, in view of the failure of the recently published multi-centre study to demonstrate any CPAP effect on mortality of patients with chronic heart failure,[50] it will be interesting to follow the development of this particular front.

The second front deals with cellular and biochemical mechanisms in sleep apnoea syndrome—oxidative stress and inflammation—that were shown to play a major role in atherogenesis in sleep apnoea patients. The 4 core papers that were included in this front[51–54] were cited 340 times. A related subject, the effects of sleep apnoea on insulin resistance, was identified as the third front with 3 core papers[55–57] cited 248 times. The fourth front includes 2 core papers and dealt with the long-term cardiovascular outcomes of sleep apnoea syndrome[58,59] cited in a relatively short time, 82 times since 2005.

Even though the identification of research fronts is a dynamic process that may change rapidly, it can be concluded that at least for the near future, sleep apnoea research will focus on the cardiovascular consequences of the syndrome. Demonstrating an association between sleep apnoea and oxidative stress, inflammatory processes and insulin resistance, as well as long-term cardiovascular outcomes of the syndrome, may result in seeing sleep apnoea as yet another major risk factor for cardiovascular morbidity.

Summary and conclusions

The present paper traced the history of sleep apnoea from the 19th century early descriptions of patients who stopped breathing during sleep to the coining of these patients as ''Pickwickian'' through their first sleep recordings by Gerardy et al. and Drachman and Gumnit, and the delineation of the nature of the syndrome by Kuhl and Yung, Gastaut and his colleagues and Lugaresi and his colleagues. It is demonstrated that the rate of publications on sleep apnoea has greatly increased in the last 40 years, reaching a peak of 854 research articles in 2006. The most influential publication in the history of sleep research is that of Young et al. published in the New England Journal of Medicine in 1993 demonstrating that 4% of men and 2% of women in the general population have sleep apnoea syndrome. The papers introducing the first treatments of sleep apnoea—nCPAP and UPPP—and the papers documenting increased mortality in sleep apnoea and its relationship with hypertension are also included among the top ten cited papers in sleep apnoea research. Cluster analysis of the bibliometric data of the last few years reveals that future research will focus on treatment effects on cardiovascular outcomes in sleep apnoea and on the pathophysiological mechanisms responsible for cardiovascular morbidity in the syndrome.

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