ResMed Origins

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Foreword

As is detailed later in this document, in 1981 Colin Sullivan and his colleagues introduced their invention of continuous positive airway pressure (CPAP) for the treatment of obstructive sleep apnea. In my opinion, the only possible rival for a single product that would produce such an upturn in life expectation and quality of life for humanity was the introduction of penicillin. Although sleep specialists were aware that obstructive sleep apnea was a very serious illness and surprisingly commonplace, it would be more than a decade after the introduction of CPAP before the true and stunningly high prevalence would be documented by Terry Young and her colleagues. Rarely in the history of medicine has an effective treatment for an illness been developed before the true magnitude of the problem was scientifically established.

The next big challenge after 1981 was to convert the Colin Sullivan vacuum cleaner device into a practical, effective, and dependable treatment for the literally millions of apnea victims around the world. Referring again to the penicillin analogy, victims on the verge of dying from pneumonia or wound infections could be miraculously restored to health by the antibiotic if it could be made very widely available. To see individuals who are failing in every aspect of their lives including their cardiovascular function and their daytime alertness restored to high energy and good health is a joy and a miracle.

The next huge challenge facing sleep professionals as well as victims of obstructive sleep apnea is the lack of effective public awareness about the problem. It remains an ongoing process to identify all the victims of sleep disordered breathing and make them aware that there is an effective treatment which will restore their lives and health. ResMed is completely committed to enhancing public awareness.

In conclusion, we must congratulate this pioneering company for its many successes, and we strongly encourage its continuing effort to improve therapeutic approaches and to support vastly expanding public awareness.

William C Dement MD PhD
Stanford University

Preface

ResMed has been conspicuous on the world business scene since it listed on the NASDAQ stock exchange in June 1995, raising US$24 million. By 2007, market capitalisation exceeded US$3 billion. Internationally, ResMed markets its products in over 80 countries. In each, it is leader in both market share and in technical excellence. For more than a decade, business assessors in the USA have recognised distinguished achievements. In Australia, its country of origin, ResMed has received accolades for design of its products and it has won awards for export sales. Its Founder has won awards from the community in Australia, and from his peers, in Australia and the USA, for leadership and professional expertise.

ResMed's business is based on devices for diagnosis and treatment of sleep disordered breathing (SDB) and its most extreme manifestation - obstructive sleep apnea (OSA) [i*]. The characteristic feature of OSA is the repeated sequence of increasingly heavy snoring, followed by cessation of breathing, with gasping arousal, and return to sleep. Consequences are insidious, increasing in severity as the disease advances. Consequences arise from mechanical damage to tissues from snoring and psychological disturbances from sleep disruption. Other mechanical effects are produced by highly variable pressure in the thorax that disrupts the heart's control of blood volume to cause nocturia. Pressure variations in the thorax also cause reflux of stomach contents into the esophagus. Frequent intermittent starving of the organs of oxygen combines with stress to cause a range of lethal cardiovascular diseases and metabolic disturbances connected to diabetes.

OSA is a disease of global significance. It is highly prevalent in every society where it has been studied. Symptoms of the disease are so conspicuous that they have been the source of comment for at least 2,000 years, yet it was only in the 1960s that physiologists recognised OSA as a distinct disease entity. Following recognition of OSA, studies of pathophysiology and the extent of its consequences were inhibited by the absence of an acceptable and successful method of treatment. With no available treatment it was difficult to establish cause and effect between symptoms and consequences.

When a scientist from the University of Sydney announced a treatment, the news was met with incredulity by the medical establishment. The equipment used for the demonstration was improvised and primitive. Theory behind the method had either not been considered by others or had been rejected without experimental testing. It took the genius of a medical scientist who was prepared to experiment and test what others had ignored or argued against, before success of this unlikely treatment was demonstrated.

Invention is only the first stage in the tortuous process of innovation. One successful demonstration is a long way from a marketable product that can be manufactured on an industrial scale. In this example, a great deal of R&D was needed to convert an improvised apparatus into an industrial product. It took determination, persistence, and the proselytising enthusiasm of an evangelist to convince financiers to invest in a R&D project of unproven utility. The requirement then was for engineers, designers, and medical researchers to create a technology that would be cost-effective and patient-acceptable. Finally, the medical profession had to be convinced and then educated, manufacturing plants built, and a global marketing infrastructure established. This gargantuan task was taken on the shoulders of one academic/engineer/industrialist.

The story told here is an acknowledgement of the resounding success of the formation and operation of the ResMed group of companies in filling every need. ResMed stands out conspicuously and favourably as a paragon against the bursting dotcom bubble. That financial disaster arose from innumerable failed attempts by others directed toward a similar goal of industrial success from academic origins. The continuing commercial success of ResMed over a

* Numbers in parenthesis in the text indicate references, identified in the Appendix. Endnotes are indicated by superscript Roman numerals.

period of almost two decades has attracted attention of scholars of business management from the level of the local high school, through government bureaucracy, to the hallowed halls of Harvard (54).

The contrary conventional wisdom of established and conservative professions combined with their innate inertia to create a variety of obstacles to the formation and eventual success of ResMed. This innovation relied heavily on the two key individuals who met and overcame all the challenges of defining an invention and taking innovation through to the global marketplace. Together they led the world into a new era of therapy with products that were commercially viable, and therapeutically effective against one of the major inflictions of humankind. Both had backgrounds that uniquely prepared them for the roles they had to play. How this came about is the main theme of this narrative. The period covered is from antiquity to 2 June 1995, when the company listed on the NASDAQ stock exchange.

The continuing success of ResMed means that this narrative considers only the first episode of a serial story that has no end in sight. This episode is concerned with the struggle to found a global organization. The next episode of growth and consolidation is left for others to cover, for the theme and challenges changed subsequent to the listing. The success of the listing was recognition that ResMed had become a mature operation, taking its place alongside other western industrial companies.

Such success would not have come without the inspired efforts of a small group of dedicated engineers and support staff. Starting as a handful, numbers increased until the organisation chart comfortably filled one page, as shown in the Appendix for 22 July 1994. In this text it is not practical to detail the contribution of each individual. It is a tribute to inspired leadership that staff relationships were harmonious, with significant achievements being made weekly. Over a score of those in Australia who brought the Company to listing are still with ResMed in 2007, when global staff numbers exceed 3000.

Of those who have left, special gratitude must be expressed to Chris Lynch. He played a critical role in the very early days, and was forced to leave only when struck down by multiple sclerosis. Ken Hely was instrumental in development of successful early masks. He also left for medical reasons. Each made greatly appreciated contributions.

On a happier note, ResMed has operated as a training ground for people seeking career advancement beyond what could be offered in-house. Congratulations to Dr Chris Roberts. With a scientific education, he gained marketing experience in another technology company before joining ResMed. No doubt the management experience he gained will serve him well in his new role as Chief Executive Officer of Cochlear - another Australian medical device success story.

A debt too is owed to Bill Nicklin, who brought the production of product substantially under one roof from a scattering of contractors. He too has moved to a senior management role in another technology start-up company. Wal Flicker worked long and hard as Company Secretary and Director and manager and operator of anything and everything to do with finance and spending and organising this and that. Shirley Sproats joined and remained until December 2005 as a most dedicated accountant, bookkeeper, personnel manager, and odd job person when the term multitasking was invented for ResCare staff activities.

The Company would not have succeeded without the dedicated efforts of these and many others.

Sherill Burden, Colin Sullivan, William Dement, and, Christian Guilleminault are thanked for photographs. Lisa and Lance Hopper and Lucy Bode prepared the design and layout for printer, John Mockridge.

Charles S Barnes PhD FTSE 26 May 2007

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OSA in Antiquity to the 20th Century

"You can't cross a chasm in two small leaps"

David Lloyd George, Former British Prime Minister

The symptom of heavy snoring is so obvious that historians had noted extreme examples in documents going back to antiquity[ii]. Notable were members of the Ptolemy dynasty that ruled Egypt for 300 years until Julius Caesar took control of Egypt (and Cleopatra) in 30 BC. Many of the Ptolemys had symptoms that are associated with OSA. Family members were recorded as being hugely obese, with indications of a genetic propensity[iii] to obesity (4). There are many other records of apparent OSA symptoms, such as heavy snoring and obesity, in prominent historical figures. These include Emperor Napoleon Bonaparte (5), Queen Victoria, US President Taft (6, with BMI >40), both Presidents Roosevelt, and Johannes Brahms, composer of a lullaby for infants (7). We can only speculate how the disease affected their reasoning, and what effect treatment would have had on history.

By the early 1800s, medical professionals were taking an interest in the interrelationships between obesity, sleep, and breathing. In those days, diagnosis had to rely on what the physician could see, hear, and feel. In 1816, William Wadd (8), Surgeon Extraordinary to King George III, wrote a critical review of current knowledge in a monograph: *Cursory Remarks on Corpulence; or Obesity Considered as a Disease: With a Critical Examination of Ancient and Modern Opinions Relative to its Causes and Cure.* In it he noted that in the obese, "respiration is performed imperfectly, or with difficulty", and that obese people "could fall asleep at any time".

The most influential description in the 1800s was not from a physician, but from the novelist Charles Dickens. In 1836-7, when he was a young man in his 20s, Dickens published a novel in serial form with the title *The Posthumous Papers of the Pickwick Club.* This made him famous as a novelist. The book can still be read on the Internet. In his novel, a conspicuous character called Joe was an excessively sleepy, red-faced, loud snoring, cognitively dysfunctional, "wonderfully fat" boy with peripheral edema. Joe's symptoms are reminiscent of OSA. Mr Pickwick himself was obese, and after imbibing too much would drop off to sleep, snoring, with choking sounds. Dickens' impact on the medical profession was substantial. Sir William Osler[iv], a Canadian who became Professor of Medicine at Oxford, was one of the most influential persons in medicine around the late 19th and early 20th centuries. Osler adopted the term Pickwickian Syndrome before the condition could be adequately diagnosed.

Scottish physician John Cheyne in 1818 and Irish physician William Stokes in 1854 described abnormal periodic breathing with central apneas, now associated with their names. The London physician, WH Broadbent (9), in 1877, gave the first detailed description by a medical professional of the clinical symptoms of obstructive sleep apnea. He described loud snoring, attributed to resistance in the pharynx, silence through two or three respiratory periods, during which there were ineffectual chest movements, and finally respiration resuming with a loud snort. He recognised the repetition of this cycle "at regular intervals, and the pause was so long as to excite attention, and indeed alarm."

Other physicians made similar observations, associating obesity with excessive sleepiness, apneas due to glottic closure, and snorting arousals. There was still confusion between sleepiness due to apnea and other sources, for example narcolepsy, which had been identified in 1880. The symptoms of narcolepsy include an uncontrollable need for sleep, even when night-time sleep was adequate. The cause of narcolepsy is still not understood, nor is there a cure[v].

Napolean

Queen Victoria

Brahms

Sleep Research in the 20th Century

"We are more prone to see what lies behind our eyes, than what lies before them"

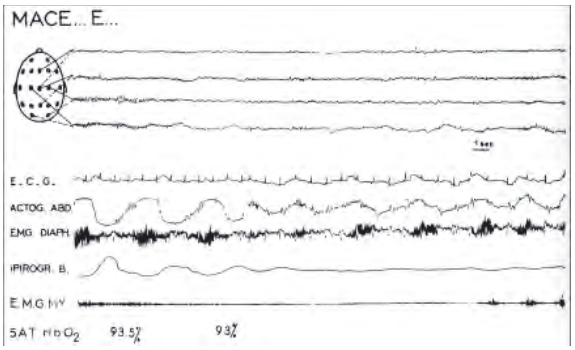
Thomas Henry Huxley 1825-1895

Introduction of electrical measuring and recording devices in the first half of the 20th century provided tools for the study of the pathophysiology and diagnosis of diseases. No longer were medical scientists constrained to short-term look, feel, and hear observations. Sleep has always been a puzzle to physiologists. Though occupying one third of a lifetime there was little understanding of why it was necessary, or how restorative functions were achieved. Instrumentation gave the opportunity for meaningful research to the many scientists trying to unravel the enigma of sleep. EEG (electroencephalo graphy), introduced in 1928, allowed the difference between brain waves during sleep and wakefulness to be recorded. At the University of Chicago in 1953 Kleitman and Aserinsky identified REM (rapid eye movement) sleep with an EOG (electro-oculogram). Kleitman went on in 1957 with a student, William Dement[vi] to find the cyclical pattern of REM with non-REM sleep, and the relationship of eye movements to body movement and dreaming.

In these days when recordings of thousands of events can be preserved on a small card, we need to be reminded that whole night studies could not be made so easily in the 1950s. Recordings were made in those days with ink on paper. Shortages of paper rolls, and the need for frequent operator attention, meant that recordings were made for short periods at intervals during the night. Dement (10) notes that such limited observations inhibited the discovery of sleep cycling, and possibly explains why his work did not attract support from other laboratories until 1959. By 1975, Hobson & McCarley at Harvard had identified specific brain areas where neurons and their associated transmitters controlled the cycle of REM and non-REM sleep.

One hundred and fifty years on from the appearance of Dickens' novel, the Pickwickian syndrome provided a strong stimulus for scientists to apply their new tools to the study of respiration in sleep. In 1956 the Pickwickian syndrome was identified as alveolar hypoventilation of obesity by Burwell and coworkers (11). Their conclusions were of limited value, as obese subjects were studied while awake. Sleep disorders were therefore missed, and somnolence was wrongly attributed to hypercapnia. The paper was probably more important in reviving interest in the Pickwickian syndrome in the research community. It was an enduring reincarnation, as since 1956 the Medline database has acquired 366 entries on Pickwickian topics, with at least four papers appearing in the first half of 2007. As sleep specialists acquired the equipment for physical measurements on sleeping subjects they began to rapidly accumulate data and make meaningful interpretations.

In 1965, French workers Gastaut, Tassinari, and Duron (12), from INSERM and the National Institute of Health and Medical Research, and Jung and Kuhlo (13) in Germany each published studies of the Pickwickian Syndrome. They recorded respiratory airflow, and thoracic and abdominal movement to recognise both obstructive and central apneas. Their work may be considered as the first multifunctional polysomnographs showing apneas during sleep. The technique remains the "gold standard" for diagnosis.



Earliest known sleep polysomnogram published by Gastaut et al in1965

When medical interest was concentrated on the Pickwickian syndrome it was the connection between obesity and cardiopulmonary comorbidities that attracted attention. In 1967-9, French and Italian workers found that obesity was not essential for OSA. At the same time, Duron et al (14) noted dysrhythmias in non-obese patients. The connection of comorbidities to sleep then became more important. That the right heart was affected was shown in France and Germany in the 1960s (for example 15). At that time, research on Pickwickian syndrome had been almost entirely in Europe and the UK. With growing appreciation of the connection between sleep and breathing, the first Symposium for sleep and respiratory specialists was held in Italy in 1972. Dement records that these events were completely ignored in the USA.

Also at that time, a French Professor of Neurology in Psychiatry, Christian Guilleminault, was showing interest in respiratory disorders during sleep. He had been a Post-doctoral Fellow at Stanford in 1970. In 1972 Guilleminault became an Associate Director of the Stanford Sleep Disorders Clinic[vii] set up by William Dement in 1970. Until Guilleminault's arrival, the Stanford Sleep Clinic had not routinely included respiratory or cardiac sensors in their night studies. Dement acknowledges (16) that Guilleminault "immediately insisted we pay more attention to sleep disordered breathing". By 1978, they demonstrated the correctness of the postulate that upper airway dilator muscles were keeping the airway open during wakefulness and were adversely affected when breathing occurred during sleep.

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Professor of Psychiatry & Behavioral Sciences
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Guilleminault, Tilkian, and Dement published the first major review on *The Sleep Apnea Syndromes* in 1976 (17). They covered the area with 93 references. By 1976, the Stanford Sleep Clinic had studied 350 people referred for sleep difficulties. Using polysomnography, sleep apnea was found in 62. From this sample Guilleminault and Dement identified apnea symptoms of snoring, a possible relationship to SIDS, abnormal body movements during sleep, sleepwalking, enuresis, morning headache with some disorientation, and excessive daytime sleepiness. They noted that there was no necessity for obesity, that males accounted for the higher proportion of sufferers, and that occurrence of some apneas was normal. It would be another 13 years before enough data had been collected and verified to justify publication in 1989 of the first edition of *Principles and Practice of Sleep Medicine* (18). This was then, and later editions have remained, the standard text on sleep medicine.

Slowly, scientists whose main interest had been restricted to sleep and its effects on health, had reason to extend their interest to disordered breathing, and its effects during sleep. Here was a whole new area of disease interactions with largely unexplored ramifications to health. There were strong hints that the heart, circulatory system, and lungs could be at risk. Research emphasis quickly shifted from Europe to universities in North America. Between 1975 and 1980, 319 articles appeared on sleep and apnea in the medical literature. That was five times as many as in all previous history. This five-year period marked the beginning of an intense era of research that still continues with increasing momentum.

Thus far it was known that the airway blockage during apnea was somewhere in the upper airway. Early workers had assumed the pharyngeal area. At the University of Texas in 1978 Remmers and co-workers (19) used pharyngeal intubation and pressure measurements to demonstrate that the locus of airway closure lay in the oropharynx, not the larynx.

One of the North American scientists becoming involved with sleep-disordered breathing was Eliot Phillipson. A Canadian, Phillipson earned his MD (1963) and Master of Science in Medicine (1965) from the University of Alberta, and gained cardiovascular experience at the University of California, San Francisco (1968-71). He joined the research and clinical staff at the University of Toronto in 1971. There, he established a reputation for his studies of respiratory control in dogs. This was "pure" or "basic" research, using an animal as a model for experiments that would not be possible on humans. In 30 years of research between 1970 and 2000, Eliot Phillipson published 40 papers. All were on breathing in dogs[viii].

To study respiration, the animal was connected to the same recording devices as were used for human polysomnography. Respiratory airflow was always important. It could be measured with a tube 10 mm in diameter inserted into the trachea through a tracheostomy[ix] – a hole cut into the windpipe to gain access to respiratory airflow. Flow was measured with a differential pressure transducer and a pneumotachograph for the rate of airflow to and from the lungs. Respiratory airflow could then be measured in response to experimental challenges, such as change in composition of respiratory gases or stimulation of the vagal nerve. By 1976, Phillipson had gained sufficient recognition to attract collaborators from research scientists in other institutions. One of these was an Australian, Dr Colin Edward Sullivan, who came as a Post-Doctoral Research Fellow from the Department of Medicine, Sydney University.

Christian Guilleminault
Professor of Psychiatry &
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Stanford University

Colin Edward Sullivan

FTSE FAA BSc(med) MB BS PhD FRACP

"One should hold one's theories by one's fingertips so that the least breeze of fact might blow them away"

Michael Faraday (1791-1867)

Dr Sullivan completed his basic medical qualifications of Bachelor of Medicine (MB) and Bachelor of Surgery (BS) in 1970, extending his medical qualifications in 1967 with a Bachelor of Science, Medicine with Honours, at the University of Sydney. He was awarded a PhD in physiology in 1977. In this period he held a research position in thoracic medicine and a clinical position as Resident Medical Officer at the Royal Prince Alfred Hospital[x] (RPAH), a major teaching hospital affiliated with the University of Sydney.

Like many Australian medical institutions, RPAH has always taken strong pride in research and in being a leader in applying new clinical procedures. One way of fostering such strategies was by exchanges of scholars with other leading research centres. Thus it was a John Read Memorial Fellowship[xi] of the Asthma Foundation of New South Wales and a Post Doctoral Research Fellowship of the Department of Medicine, Sydney University that took Sullivan to Phillipson's laboratory.

Arriving in Toronto, Colin Sullivan had a strong background in physiology, particularly of the respiratory system, and in clinical medicine. The academic atmosphere at the University imbued him with a passion for acquiring knowledge through research. In the laboratory at Toronto, Sullivan's work was with effects such as hypoxia, hypercapnia, control mechanisms during REM and non-REM sleep, arousal, and laryngeal stimulation. All this was on the respiratory system of dogs.

In 1978, Sullivan received the Cecile Lehman Mayer Research Award[xii] of the American College of Chest Physicians for original research on the influence of

Colin E Sullivan
Professor of Medicine
University of Sydney

sleep on airway smooth muscle tone. He had joined the thin ranks of scientists working on sleep and breathing.

In 1979 Sullivan returned as a Senior Lecturer to the University of Sydney, where he continued working with dogs, and, importantly, resumed clinical treatment of patients.

Sullivan had a long-term interest in the role of the upper airway in cot death, often called SIDS, an acronym for the descriptive term sudden infant death syndrome. Dogs were used as a model for measuring and comparing responses to nasal and tracheal occlusion. Now, instead of entering the airway though a tracheotomy, as was done in Toronto, Sullivan devised a method for using the entire normal respiratory tract, including the nose. To do this, a fibreglass mask was moulded to fit over the dog's snout. It was glued in place with silicone adhesive, which also ensured an airtight seal. Air, or other experimental gas, could then be delivered through the mask directly into the nose to contact the whole airway. Similarly, sensors or other instrumentation could be located in the mask to react to respiratory airflow (22).

In his review, *Disorders of Breathing in Sleep*, published in 1980 (23), Sullivan was able to identify 6 major disorders. These were described as OSA, snoring, central sleep apnea and hypoventilation, Cheyne-Stokes breathing, REM-sleep-coupled arterial haemoglobin oxygen desaturation in chronic lung

disease, and sudden infant death syndrome. Obesity was recognised as a predisposing factor. Interestingly, Sullivan hypothesised that the reverse could also be true, that is, that OSA could contribute to obesity. This was based on sleep time in animals. In 1999 his hypothesis received support when CPAP was shown to reduce leptin levels in obese OSA sufferers. Subsequently there have been several confirmatory and extending studies of effects of OSA and CPAP on leptin and other appetite-moderating hormones.

In 1980, Sullivan could point to a spectrum of clinical consequences of OSA. He listed noisy snoring, excessive daytime sleepiness, intellectual and personality changes (including depression), pulmonary hypertension, right heart failure, systemic hypertension, nocturnal arrhythmias, abnormal nocturnal motor activity (choking and panic attacks), morning headache, unexplained polycythemia, and sudden unexpected nocturnal death. These are all serious conditions needing treatment, or preferably, prevention.

By 1980, the medical research community working on sleep-disordered breathing was well aware that they were in an area of immense potential. However, this knowledge was effectively confined to a relatively small group of elite research scientists. Among the research community interest and dedication had become intense, tinged with a high degree of competition to be first with significant findings.

Patients being studied were not representative of the community at large, as most had been referred to major teaching hospitals or specialist clinics because of the severity or unusual character of their conditions. Little was known of the cause of any of the disorders of breathing during sleep. Apart from these specialist research scientists, there was still very little knowledge in the community or among primary care physicians of the prevalence of these disorders, or the extent of their long-term effect on morbidity or mortality[xiii].

University medical courses had little if any content on sleep and no teaching on breathing during sleep to alert primary care physicians to the dangers of snoring. It was clear that much fundamental research would be needed before a basic understanding could be gained on all these matters. Many years would pass before knowledge of sleep-disordered breathing filtered through to primary care physicians.

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Nasal CPAP

"We must all obey the great law of change
It is the most powerful law of nature"

Edmund Burke (1729-97)

In April 1981, Professor Colin Sullivan startled the research community with a paper (34) in the April addition of the prestigious English medical journal *Lancet*[xiv]. It carried the title *Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares*. The paper described successful treatment of five OSA patients by maintaining a continuous pressure of air into the patient's nostrils during sleep. On application of pressure each patient immediately experienced normal sleep, with loss of excessive daytime sleepiness and other symptoms. That air pressure was the cause of loss of apneas was shown by stopping the airflow, whereupon apneas resumed at the same rate as before treatment. Sullivan assumed that the air pressure had acted as a splint to hold open the occluded airway.

At the time, this was not a simple experiment. An airtight seal had to be maintained in the nose for periods of about 8 hours of sleep, during which movements of the head would be frequent. Sullivan's solution was to improvise a nasal mask from equipment easily accessible in a hospital workshop, using experience gained from his dog experiments. In this first series of experiments, airflow was generated from a vacuum cleaner motor. A flexible tube took the air to a rigid wide-bore plastic tube acting as a manifold, and held firmly under the nose by a headgear. From the manifold, two soft silicone tubes entered the nostrils. An airtight seal was achieved by gluing the tubes in place with silicone adhesive (Dow Corning 382). Expiratory airflow passed to a tube with a manually controlled constriction, varied to adjust pressure up to about 10 cm water, as measured on a manometer. Other tubes could be inserted into the manifold to sample expiratory gasses for CO_2 assay.

Results were brilliant, demonstrating total elimination of an intractable, progressive disease that had defied all previous non-invasive methods of treatment. Instead of rejoicing, the medical community was sceptical. As demonstrated, the method was not simple to apply, and early reports failed to confirm the results. For example, with the confidence stemming from treatment of four patients, a group from the New York Hospital–Cornell Medical Center (35) said that their "experience thus far suggests that nasal continuous positive airway pressure will often fail or be impractical". Their experiences detailed in the paper certainly justified this conclusion. One patient needed constant nursing attention each night before finally giving up treatment, a second received no treatment because she could not go to sleep at all when fitted with the equipment, a third had 134 apneas per hour despite receiving 15 cm of CPAP, and the fourth slept fitfully for approximately three hours before he suddenly sat up screaming and tore off the mask.

No clinician would risk inflicting that treatment on his patients.

Over a year was to pass before David Rapoport at New York University, fully confirmed Sullivan's results (36).

Another reason for scepticism became apparent later. A form of continuous positive airways pressure was already being applied to infants suffering from acute respiratory distress arising from apnea of prematurity. This was a disease of different etiology from OSA. The novelty of Sullivan's approach was that delivery of air pressure was restricted to the nose, not the whole face. The reason why the medical community was stunned by the success of this approach became apparent in 1984. In that year, a group of the most experienced pulmonologists in the USA met at a clinical conference to consider factors influencing upper airway closure. They reported (37) that

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Of all the devices that have been used in attempting to keep the upper airway open, the one that shows the most promise is nasal CPAP. …It is hard to understand why all the air blown into the nose does not come out the mouth, but it does not. … It appears that this device is 100 percent effective.

Sullivan's troubles were not over. He was working in a big university, competing with other academics for limited funds, administered by a blinkered and self-serving bureaucracy. As it was demonstrated, his method was not practical outside a research hospital. Apart from a relatively few specialist research scientists in the USA, there was little interest among medical clinicians. Those OSA sufferers unfortunate enough to enter the medical literature were extremely rare. No death certificate had ever indicated OSA as a cause of death. Even today, when OSA is known to have major associations with mortality and morbidity, there is only one record (38) of OSA as a cause of death. There was still no idea of the prevalence of OSA in the community. Numbers of patients reaching specialist clinics were insignificant in the broader scheme of public health. There were so few medical specialists active with respiration during sleep that the position was not going to change quickly. On the face of it, there was no reason for a change to a more favourable therapeutic attitude toward the disease.

In Australia, medical research funds mainly come from the Federal Government, acting on advice from the National Health and Medical Research Council (NHMRC). Applications from research scientists are subjected to peer review by a selection committee. Through this process, relatively large funds have been lavished on world-class research institutions flourishing in all capital cities. Clinical scientists in university hospitals have also benefited. The value to science of these grants is demonstrated by the awarding of Nobel prizes to brain researchers, immunologists, biochemists, and microbiologists.

Sullivan's applications for research grants from NHMRC were repeatedly rejected by his peers.

In 1990, the Federal Government established Cooperative Research Centres (CRC) with the intention of encouraging institutions and Government laboratories to collaborate with industry to obtain commercial products from basic or applied research. Sullivan was unsuccessful in several applications for CRC support for his apnea studies.

For several years after his 1981 publication, Sullivan was forced to rely heavily on one technician working with clinical staff toward practical CPAP equipment. Following his experience with masks glued to dog's noses, Sullivan's next human mask development started with the making of a plaster cast of each patient's nose. From this, a fibreglass cover was made to precisely fit over each individual nose. Air inlets and outlets were then fitted to a manifold that was attached to the fibreglass nose cover to form a mask. Each night this was glued over the nose with silicone adhesive. In the morning the whole mask was peeled off and cleaned for reuse. Three hundred and fifty patients were treated successfully with the glue-on mask.

The first commercial airflow generator had a 60 W 240V AC motor, driving a vortex blower[xv], designed for a spa-bath. It weighed a robust 6.75 kg. Its power was sufficient to allow location of the noisy motor in a room distant from the bedroom. For comparison, the latest ResMed flow generator, the S8, weighs in at 1.3 kg, and is quiet enough to be next to the sleeper, without disturbing him or his partner. By 1989, when ResMed introduced a more suitable motor, Sullivan had 1,000 patients using the vortex blower[xvi].

With Sullivan's results confirmed, and effective equipment becoming available, there was steadily increasing interest and involvement from the international medical community into OSA and its

effects. In the five years from 1981 to 1985, over 1,400 entries on "apnea" appear in Medline. Also, industry was taking notice. In 1986, the American company, Respironics, began selling a CPAP device in North America.

With research and commercial developments moving swiftly overseas, and his own resources limited, Sullivan could see that he was being forced into a minor role in a burgeoning research area that had been opened up by his own efforts. Respironics and some other US companies with respiratory interests had made approaches to him. These were rejected, as he wanted future developments to be in Australia.

The future looked bleak – until he met Peter Farrell.

Glue-on nasal mask

Without humidifier	Vortex 1981	R2 1988	APD1 1989	S7 2002	S8 2005
Length mm	240	230	325	270	145
Width mm	215	320	230	230	164
Height mm	250	248	240	142	117
Weight kg	6.75	6.9	4.3	2.3	1.3
With Humidifier	NA	NA	NA		
Length mm				372	315
Width mm				230	145
Height mm				142	118
Weight kg				3.2	1.95

Dimensions of flow generators

Peter Craig Farrell

AM FTSE BE SM PHD DSc

"Technology is the turbocharger of economic growth; it always has been & always will be"

Peter C Farrell

In the 1960s, while Colin Sullivan was developing academic skills in physiology at Sydney University, Peter Farrell was at the same university becoming expert in the academic and practical skills of chemical engineering. In those days Sydney University was an institution with large numbers of Faculty and students, spread across a broad Campus. There was little reason for personal contact between the two young scientists working under the pressure of undergraduate study, to be followed by junior research fellowships in different Faculties. Neither had settled into a stable career path. Though their lives were separate, their life styles shared similar qualities including a strong dedication to the creation of new knowledge and the ambition to be best in the world in their fields.

Following graduation in Sydney in 1964 with a bachelor's degree in chemical engineering, Peter Farrell studied at the Massachusetts Institute of Technology during 1966 and 1967 to earn an SM degree in chemical engineering. He worked at Chevron for a year before returning to MIT as an Industrial Liaison Officer during 1968-70. Moving on to the University of Washington, Seattle, Farrell concentrated his research interests into bioengineering, obtaining a PhD and joining the Faculty as an Assistant Professor. He was awarded a DSc from the University of New South Wales in 1981.

In the 1960s, biomedical engineering was beginning to be recognised as a specialist area within engineering. At Washington, Farrell could collaborate with a medical group that had been leading the world in treatment of end-stage renal disease[xvii]. Belding Scribner had been appointed to the Medical faculty of the University of Washington, Seattle, in 1951. Scribner, in 1960, introduced a permanent external Teflon shunt between the artery and vein used in hemodialysis.

Dr Peter C Farrell AM
President and CEO ResMed group

This made it easier to connect the patient to the dialysis machine. In 1960, Dr Fred Boen joined the Department. He had made advances that brought peritoneal dialysis to the home. A continuing difficulty was in gaining permanent access to the peritoneal cavity without introducing infections. In 1963 Henry Tenckhoff developed a successful system to routinely operate peritoneal dialysis. The key feature was a silicone catheter tube with Dacron cuffs at the points where the tube penetrated the peritoneum. These allowed ingrowth of tissue to create a permanent seal that resisted infection. The patient could then be mobile while dialysis continued. This became known as continuous ambulatory peritoneal dialysis or CAPD. The three-bed Seattle Artificial Kidney Center, opened by Scribner in 1962 was the first free-standing dialysis center in the world.

A lesson learned was that a mature medical technology that looks absurdly simple at first sight, may have been incredibly difficult to develop from a concept into a treatment that is easily applied, accepted by the patient, and is therapeutically effective. At Washington, Farrell was exposed to the trials, tribulations, and satisfaction in leading the world into application of a new, lifesaving, technology. These were lessons well learned, acting to wind up the spring of apprehension, to be released if a comparable opportunity arose.

With his Doctorate duly complete, in 1972 Peter Farrell returned to Sydney as a Lecturer in the Department of Chemical Engineering the University of New South Wales[xviii]. There he established a research group, continuing to work on topics around end-stage renal disease, with particular reference to continuous ambulatory peritoneal dialysis (CAPD). However there was still work to be done on hemodialysis[xix].

Apart from his science, Farrell could see much that needed attention in university management, not to mention industry, and society at large. He was not one to criticise and ignore. As a compulsive worker and achiever, he was, and still is, willing to suggest and help implement political and social change for the betterment of the individual and society[xx].

The University had well-established departments of biology, microbiology, biochemistry, biotechnology, and medicine. Farrell noted a deficiency in the enabling technology of biomedical engineering. He was instrumental in establishing in 1978 a Graduate School of Biomedical Engineering, in which he held the position of Founding Director. Within the School his work continued, mainly around end-stage renal disease and its treatment by hemodialysis and CAPD. A total of several score refereed papers were published on these topics from 1970 onward.

In the USA, Baxter Healthcare, a dynamic company that had been based on manufacture of blood products and intravenous solutions, had been collaborating on renal topics with Willem Kolff and others since the 1950s. The company had established a renal division in which CAPD had achieved the status of a core component. By the 1970s Baxter had developed expertise in flexible plastic bags to handle sterile intravenous solutions and blood products. The requirement for peritoneal dialysis solutions in flexible bags fitted so well into their operations that sales of CAPD products reached $1 billion in 1978. This was contributing to a 20% per year growth that was maintained for a 20 year period. As a science-based company Baxter had established research laboratories in Illinois in 1969. In addition, as a multinational company, they needed international research facilities. In 1984 Peter Farrell was appointed a Vice President Research & Development of Baxter Healthcare Corporation. His first task was to establish a research laboratory in Tokyo. This he did while retaining Directorship of the Centre for Biomedical Engineering.

At this stage Baxter was a high technology company with a high growth rate. Growth came from acquisition in addition to internal developments. In 1985 Baxter acquired American Hospital Supply Corporation, to become a broad-based health-care products distributor in addition to a developer of medical technologies. It was then, and has remained, the world's largest hospital supply company. There was an obvious symbiosis between Baxter, the company, and Farrell, the individual. Both were aggressively but ethically growth orientated, both were highly technically competent in their areas of specialty, and both were going to succeed in improving society by their own endeavours, not at the expense of others. In all, the partnership was a classic example of the best aspects of capitalism in action.

With the successful establishment of the Tokyo laboratory, after an absence of 18 months, Farrell returned to Sydney. His vision now had extended beyond the Centre for Biomedical Engineering to include the future of Australian academic and institutional research. The strategy would be to use the Baxter connection to establish a company-sponsored research group to collaborate toward the commercialisation of promising projects. To this end, he formed the Baxter Centre for Medical Research (BCMR) in 1986.

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Baxter Centre for Medical Research[xxi] 1986 -1989

"Creativity is thinking up new things INNOVATION is doing new things"

Theodore Levitt/HBS

Beginning in mid-1986, Peter Farrell recruited a nucleus of scientists and engineers, accommodating them in an office building in a suburban industrial area. The intention was to eventually become involved in the commercialisation of projects that were showing promise of medical application but were lacking development resources. Australia was then, and still is, renowned for the quality of its medical research conducted in institutions and teaching hospitals in each state. In total, the volume of high quality research was substantial, making a very significant contribution to world medical knowledge[xxii].

It did not take long for the activities of the embryonic development company to become known among the academic and government research laboratories. A number of collaborations were formed[xxiii], with Baxter financing projects in hospitals and universities. With some of these, Farrell was able to extend his studies of end-stage renal disease.

Colin Sullivan had unsuccessfully sought local support for some time before he approached Peter Farrell. If local ownership of his technology was Sullivan's first priority, BCMR would not seem to be an ideal candidate. Despite Peter Farrell's nationalism, the ultimate owner of BCMR was a multinational. Against this, the research and commercial development would be close to Sullivan's laboratories and clinics. Peter Farrell had a proven record of achievement in academia and in development of medical technologies, and he was well known and respected in science and technology circles.

Sullivan's method of demonstrating his CPAP technique was by video. It showed an obese male in bed, writhing, suffocating, snorting, and gasping in the potentially fatal grip of advanced obstructive sleep apnea. When CPAP was turned on, the scene changed immediately and dramatically to a large male sleeping peacefully.

Farrell was convinced.
He included CPAP development as a project for BCMR.

It was a fateful decision. As Vice President of R&D of Baxter Healthcare, Director of the Baxter Centre for Medical Research, and Director of the Centre for Biomedical Engineering of the University of New South Wales Peter Farrell had personal experience and access to resources that were ideally suited to this project. If Sullivan epitomised the best in inventive academic science, Farrell epitomised the most accomplished industrial scientist. Collaboration would have to succeed.

But there were real dangers, unrecognised, growing, and unavoidable.

Here was a project on a subject not widely accepted as medically important in the community, that is, among potential customers. There was not a shred of evidence on the size of the market, and there was already an established, albeit small, company selling a functional product. If Baxter were to enter the market it would have to be quick, and its product would have to be superior to one already effective, made by a company that had been established for a decade. On a more positive note, the large multinational Baxter had a respiratory therapy division in which a CPAP product could be accommodated and actively promoted. The parent could also provide funding, virtually unlimited, if the need were demonstrated. First, BCMR would have to show that they could devise a superior device.

Even before collaboration on technology could begin, there were difficulties. For generations, Australian

universities, like their British counterparts, had been Ivory Towers[xxiv], preoccupied with lofty, remote, or intellectual considerations rather than practical everyday life, populated by an elite, and funded from the public purse. With increasing numbers of undergraduates seeking vocational benefit from tertiary education, and increasing cost of research demanded by an industrial society, universities were now seeking to broaden their financial base. American universities had shown that making money from exploitation of research results was no impediment to academic excellence. Sydney University had responded to changing attitudes by establishing a Business Liaison Office, where staff would assist academics protect intellectual property arising from their research, and negotiate with industry on financial rewards for the inventors and the University.

In addition to his Lancet publication disclosing his method of treating obstructive sleep apnea, Sullivan had sought assistance from the University's Business Liaison Office for obtaining patent protection of his invention. This request was declined. Sullivan then used his own resources, through his private company, Somed Pty Ltd, to patent a *"Device for treating snoring sickness"* that issued as AU 560,360 independently of the University.

When it came to commercial negotiations with BCMR, Sullivan was required to be represented by the University's Business Liaison Office. The position was complicated because the Business Liaison Office would normally make a public call for tenders, and choose the one most favourable to the inventor. With tenders received in confidence by the University, this procedure would have provided a level of uncertainty for BCMR. With this patent, the inventor was seeking collaboration with an Australian company. BCMR might be an organization operating in Australia, but it was entirely owned, as the name showed, by a foreign company. BCMR's General Manager, Christopher Lynch[xxv], had to lead delicate negotiations, with assistance of solicitors, to arrange a deal that allowed the collaboration to proceed. It was a credit to all concerned that a deal was struck. Baxter purchased the patent, and agreed to pay royalties to the inventor for a period of 5 years.

Meanwhile, overseas interest in CPAP continued to grow. Other companies from the USA were showing interest in obtaining collaborations with Professor Sullivan. Respironics was notable, as they had begun to sell a device in 1985. Gerald E McGinnis, who had formed Respironics in 1976, approached Sullivan in 1986, seeking collaboration. Sullivan had declined. This was a good decision, though it may have been made for the wrong reasons. In the event, Sullivan and his work were to benefit substantially from a local collaboration. Later events showed a very different outcome may have arisen if he taken the proposed course by Respironics. Other interested parties contacting Sullivan were Puritan Bennett from the USA, and SEFAM from France.

Since his proof of concept of nasal CPAP in 1981, Sullivan had used his limited resources at the University to make valuable progress towards commercially useful equipment. With his one technician, Jim Bruderer[xxvi], to build equipment, progress was always going to be slow. By 1986 they had devised a reusable mask that did not require gluing to the nose each night. It consisted of a silicone rubber "cushion" to make airtight contact with the face. The cushion was fixed to a rigid plastic frame, held in place by a headgear of flexible straps. Though functional, the design was not optimal for volume production.

The massive vortex blower was providing sterling service as a flow generator. It was now being used by 1000 patients. Again, this was a therapeutically functional device, but rather unsuitable as a commercial product[xxvii].

Vortex Blower with Sullivan/Bruderer Soft Mask

If BCMR were to be successful in the marketplace, there were two urgent needs. Both a flow generator and a mask system had to be designed to be suited to factory production and to be widely accepted by patients. In-house facilities for these advanced development phases were non-existent, or at best, were inadequate. They would have to rely to a large extent on contractors.

At the time there was little knowledge of actual airflow requirements. There were no data on clinical significance of pressure swings between inspiration and expiration, nor what level would be acceptable. Pressure swings were thought to be undesirable, and would be hard to avoid. A balance would have to be maintained between a high flow rate to minimise swings, and the weight and power of the motor required to provide such an airflow. From an engineering viewpoint, the vortex blower presumably had adequate capacity. It was never designed for bedroom use and could not easily be adapted to an aesthetic appearance or a noise level acceptable to a pair of nearby sleepers. A more acceptable flow generator would need to be designed from first principles.

With little experience to guide them, and no time for basic research, Lynch, with engineer Phil Hone, rejected the vortex approach in favour of a centrifugal fan[xxviii]. A tangential fan would be quieter, but would be too bulky. An axial fan could have supplied volume, without good control of pressure. To minimise pressure swings a three-stage, metal, 125 mm diameter centrifugal fan was designed. This was driven by direct connection to the motor, rather than by belts, as in some early vortex blowers. A 12V 50W DC flat commutator (brushed) motor with a variable speed drive was selected. Prototypes were made by a father and son contracting team working from their garage in a Sydney suburb. One was a mechanical engineer, the other an electrical engineer. The first complete unit, known internally as the R1, had a metal case. The small company was not equipped for larger scale production. For commercial scale production, an electrical goods manufacturing company in Melbourne produced the same mechanism in a custom-made metal casing. The original link between motor and impeller was with rubber tubing. This was not durable and was soon replaced by a coil spring. It was known internally as the R2, and marketed by Baxter in 1988 and 1989 as the Sullivan nasal CPAP System.

Motor and Fan 1988 and 2006

Sullivan Nasal CPAP System (R2) 1988

Engineer Phil Lutton studied acoustical and rebreathing properties of mask design. Sullivan's original concept had a large diameter outlet for rapid removal of exhaled breath to prevent rebreathing. This was changed to a small outlet with vents that had acceptable acoustic and rebreathing properties. By September 1988 Lynch and engineer Ken Hely had redesigned Sullivan's reusable mask system for large-scale production. Cushions were made as independent units, separate from the frame, in three sizes to fit noses of different shapes and sizes. Cushion design allowed detachable fitting of each size to the one-sized frame. Known as Series 1, cushions were made by a contracting company TQM (for Total Quality Manufacturing[xxix]) for sale with the Sullivan Nasal CPAP System. This design remained in service until 2005 – a great tribute to its serviceability.

Breathing against CPAP pressure requires extra effort, causing some people to have difficulty falling asleep. Collaborative research between Sullivan and Lynch led to the delay timer patent (PCT/AU88/00 8 Sep 87) issuing as US patent 5,199,424 on 6 April 1993. This feature would provide an initial low pressure, to allow the patient to go to sleep, followed by a pressure gradually rising, over a selectable time period, to the full therapeutic level.

Mask Cushion Series 1

Series 1 Mask Frame

In these early years foundations were laid for another patent to issue later. It was recognised that there is a time lapse after going to sleep before apneas occur, that there are periods of sleep when apneas do not occur, that therapeutic pressures may differ between apnea events during one night, and that pressure needs could vary from night to night. This raised the possibility that if an impending apnea could be anticipated before it became clinically significant, air pressure would only need to be applied to prevent the apnea developing. Advantages would be two-fold. There would be periods when no elevated, therapeutic pressure was needed, and, presumably, pressure to prevent an impending apnea would be lower than that required to remove an established apnea. The patient would have more rewarding sleep through fewer arousals, and lower average delivered pressure during the night, with expected better compliance and hence more effective therapy.

Most apneas are preceded by snoring. Colin Sullivan suggested that snore detection by a microphone in the mask could be used to signal when an apnea was developing, and an increase in pressure was needed.

At the time, the few BCMR staff were fully engaged in production and marketing. It was one of Colin Sullivan's patients, Michel Calluaud[xxx], who was called on to design and make a prototype. Calluaud had experience in design of aircraft navigation instruments and computer control of industrial processes. As a long-time wearer of the glue-on mask he was familiar with apnea treatment. At the time he had access to an equipped workshop at a technological museum. The principle of operation that was decided upon was that if two snores were detected within a set time period, pressure would increase. Subsequent snores would trigger a further increment. This pressure continued until snoring was eliminated, or until a safe maximum pressure was reached. After a period of no snore, pressure would be reduced. All time variables were preset.

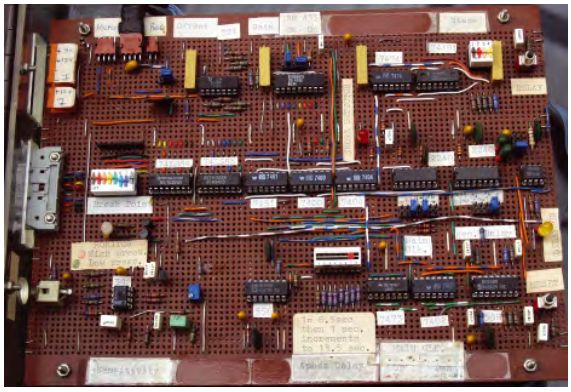
A trial on 12 patients was organised by engineer Phil Hone through the Sleep Apnea Research Association - a community group of CPAP users. Treatment worked successfully on two patients, but had various deficiencies with others. The conclusion was that the

concept had merit, but snoring was not a sufficiently sensitive trigger for pressure change. With more pressing problems demanding attention, there was no further work on this approach for the time being.

One of the disturbing matters that had been simmering in the background came to public attention on the 6th of May 1989. On that day, the Sydney Morning Herald carried an article with a headline that read, "$10m deal linking uni, US business collapses." It sounded the death knell for BCMR. The article announced the demise of BCMR because the parent company had decided to concentrate all of its research into their US Facility at Round Lake, near Chicago. The 16 BCMR staff employed at the time would be assisted to relocate or be paid off. Baxter was generous in continuing support for most of the established projects. Renal projects were passed on to the Centre for Biomedical Engineering. Others were taken over at Baxter's Round Lake facility.

Baxter had recently sold its respiratory therapy division and had no interest in sleep-disordered breathing. The OSA project became the unwanted orphan.

For Peter Farrell there were two options. One - he could relocate to the USA and remain in the highly paid, relatively safe, prestigious position of Vice President of R&D in a major company; or two - he could walk away as an unemployed ex-senior executive. Baxter offered help. For a small consideration he could take his partly developed OSA project with him and build a new company. The risk would be huge. The product was barely past the prototype stage, there was no income, no manufacturing facilities, no staff, the market size was not known, medical professionals who would have to prescribe the product were largely unaware of its existence, few were convinced of the need for OSA treatment. The corporate landscape is littered with failed ventures that started with far superior resources and prospects.
He took option two.



Snore detection for pressure control 1986

Michel Calluaud 2003

ResCare

"Even if you're on the right track,
you'll get run over if you just sit there"

Will Rogers, US humorist & showman (1879 - 1935)

Farrell's plan was for a management buy-out of BCMR.

It is not expensive to set up the legal framework to permit a company to trade. As a start Farrell put in his own money, and obtained a commitment from the few senior staff who were to join him. This part was easy. A legal entity was established.

To pay salaries and fund operations brings in a whole new and larger ongoing demand for cash. Start-up companies often obtain finance from venture capital companies. The disadvantages are that financiers usually require some measure of control of the company. Also, they need to be satisfied that there will be a reasonable rate of return on their outlay within a reasonable time frame. Instead of this option, Peter Farrell was able to convince some individuals, termed Angel investors in the jargon of industry, to provide loans and equity, that is, to become shareholders holding company debts. In total, A$1.2 million was raised and ResCare Holdings Limited was registered in Sydney in August 1989. This was a legal public entity complying with company legislation, in which shares could be held and traded, but it was not listed on a stock exchange.

Initial Directors were Peter C Farrell (Chairman), Ross Harricks (a Director of a medical device company), Michael Hirshorn (Director of a venture capital company), Christopher E Lynch (Executive Director), Christopher G Roberts (Executive of a medical device manufacturer, and former student of Professor Farrell), Robert Sauer (Lawyer), and Colin E Sullivan. Company Secretary was Walter Flicker[xxxi], a former student of Professor Farrell.

Baxter was sympathetic. For an initial cash outlay of A$558,000 on 16 August 1989, ResCare acquired the assets relating to sleep apnea treatment held by Baxter Healthcare Pty Ltd. These included Sullivan's original patent, and intellectual property subsequently developed by BCMR.

Initial staff of ResCare were Peter C Farrell Chairman and Chief Executive Officer; Christopher E Lynch, General Manager; Walter Flicker, Company Secretary; engineers Michel Calluaud, Ken Hely, and Phil Hone, nurse Sherrill Burden[xxxii], sales and marketing; with Analie Singh as Office secretary.

The position of the fledgling company was precarious. The only marketable product was not much more than an advanced prototype, market size was still not known, there was little working capital, a lack of infrastructure, and negligible manufacturing facilities. Production was through contractors, usually small companies prepared to take risks. Marketing and selling began with Sherrill Burden, a renal nurse, who was running trials on infection control with continuous ambulatory peritoneal dialysis. While doing her rounds of patients enrolled in trials in Sydney and New Zealand, she was able to contact respiratory physicians. For User Manuals, she printed instructions on glossy A4-size paper obtained from the

APD1

APD2 and Bubble Mask in use

Examination by Peter Farrelll and Chris Lynch

local stationary store. Pages were then folded in half and stapled to form an A5-sized book. The feedback obtained from these excursions was encouraging for sales. Many renal patients had severe OSA[xxxiii].

Before sales could be made in the major markets of USA and Europe, the product had to meet regulatory requirements of each country. Chris Lynch travelled the world, finding out FDA requirements in the USA and electromedical standards in Sweden. Potential distributors were visited in UK, Sweden, and Germany, where a lasting relationship was formed with Dieter W Priess of Priess Med Technik. Back at base, manuals had to be produced, giving relevant precautions and warnings.

During the first year there were frantic efforts to revise and amend the technology. The metal case of the Sullivan Nasal CPAP System (R2) was soon seen as a hazard. To provide the prescribed pressure involved adjustment of motor speed with a screwdriver working near live wires. During 1989, engineer Phil Hone worked with a professional design company, Schremmer Crick & Associates, to design and create a plastic case. ResCare's resources were so limited that he spent most of his time in the offices of the contractor. The shape of the redesigned device was determined to a large extent by the need to accommodate the voluminous three-stage fan. The end product was essentially a cube. It included a delay timer, a pressure indicator, and a switch-mode power supply. Small numbers were manufactured under contract in Melbourne (by Neutronics). The arrangement was unsatisfactory. Subsequently, larger numbers were made (by McNaught) in Sydney. It was released in September 1989 as the APD1 in Australia, and later the USA through ResCare Inc and in Scandinavia. About 800 units were produced at the rate of 50 per month under the supervision of Bill Nicklin[xxxiv]. It ranked as the first commercially viable product of the Company.

Encouragement came at the end of the first financial year of 30 June 1990, during which sales revenue of A$1 million was achieved, and staff numbers reached nine. Significantly, 25% of product was being exported. An operating loss was expected, and at A$230k was manageable. At this stage, there was no competing product in the Australian market. A feeling of comfort came from the knowledge that ownership of Professor Sullivan's basic patent on nasal CPAP (AU 560,360) gave ResCare the formidable protection of the Law from unfair competition. The Delay Timer (US 5,199,424) and Auto Feedback (US 5,245,995) patents arising from collaboration between Colin Sullivan and Chris Lynch were assigned to ResCare.

The Federal Government of Australia had systems to encourage industrial R&D and to assist companies to become established. In 1989 an R&D grant for $150k was received from the Industrial Research and Development Board. This was followed in 1990 by an International Business Development Grant of $110k from Austrade, the Government's department to assist exporters. These grants could not have come at a better time. They were put to good use.

On the technical side, two developments allowed a major advance in flow generator design. First, brushless DC electric motors were just becoming available in quantity in 1989. Michel Calluaud located a product from PAPST in Germany that was suitable. Replacement of the carbon-brushed flat motor allowed some reduction in size and weight.

Rear:Flow Generators Vortex, APD1 1989, Sullivan Nasal CPAP System (1988)
Front:APD2 (1991)

82 Waterloo Road North Ryde

An even greater benefit came from reducing the size and weight of the impeller. The much faster (10,000 RPM) rotational speed of the brushless DC motor permitted redesign of the impeller to a single stage 95 mm impeller made of polycarbonate. Now the impeller was attached directly to the rotor, obviating need for a drive shaft.

The greatly reduced size and weight of this combination of brushless DC motor, with a smaller single stage impeller, allowed a redesign of the flow generator housing. The new design created by a commercial design company came as the APD2 for release in April 1991. Smaller internal components allowed a case with a lower profile. A new style incorporated a carrying handle as an integral part of the case. This styling characterised subsequent flow generators through to the S7 in 2002.

These advances confirmed ResCare's technical superiority over the competition.

Meanwhile Sullivan and Bruderer had made the next advance in mask design, filing the Bubble Cushion™ nasal mask patent in their joint names on 21 May 1990, from which it issued as US 5,243,971 in September 1993. The University of Sydney retained ownership of the patent and gave ResCare an exclusive license. In ResMed's hands, the Bubble Cushion was known as Series 2. The cushion retained the firm form of the Series 1, and fitted the standard frame and headgear. Added to the firm face-deforming cushion was a thin silicone rubber[xxxv] film that made a larger area of contact with the facial skin when inflated by air. This allowed flexibility, to give a superior rolling seal that was retained more readily during head movement. Bubble masks were incredibly successful, selling in six times the numbers as ResCare's flow generators, suggesting that many must have been used with competitor's flow generators. In Germany, Priess Med Technik referred to it as the *Universalmaske*.

Sales during financial year ending 30 June 1991 were twice those of the previous year. An Australian Government National Procurement Development Grant of $489k dollar-for-dollar was received. It was possible to retire a $500k loan.

There was loss of $146,600 for financial year 1991. Some of this was due to unbudgeted legal fees incurred during formation of a strategic relationship with the major medical device company, Medtronic. The agreement made in October 1990, was for an investment by Medtronic of US$1 million in ResCare equity. Shares at the time had a par value of 50 cents, though notionally worth about $6.50. In addition, Medtronic required that it be given a 3-year option, expiring in 1993, to acquire all of ResCare's assets for a price of about $30 million. In return, Medtronic had a 5-year exclusive license to distribute ResCare products in the USA, and in the Benelux, France and Italy. ResCare already had exclusive distributors in the UK, Scandinavia, South East Asia, and some other countries.

At the end of financial year 30 June 1991 there was much cause for optimism. Products had improved markedly. The new flow generator was well received when launched at the American Professional Sleep Societies meeting in Toronto. Sales were doubling each year to reach a substantial total. Business was looking good, and while ResCare held four key patents it had every reason to think that good times would continue. ResCare had come to favourable

CPAPs being loaded for export watched by Bill Nicklin 1993

Brian Dibblee supervising loading of first export container August 1994

attention of the business world through gaining the International Business Achievement Award from the Federal Government's Austrade department. The future looked so bright, that guidance was given for another doubling of revenues in the coming year.

During financial year ending June 1992, sales revenue did indeed more than double – from A$2.11 million in 1991 to A$4.36 million in 1992. Exports increased from 25% up to 50% of total sales. Profit for the year was A$552k, as opposed to the loss of the previous year. Much of the increase in profit came from Germany, where the distributor, Priess Med Technik, had become leading CPAP supplier, with market share of 50%. Distributors in Sweden and the UK were also doing well, and new distributors were added in Belgium, France, Holland, Italy, Spain, and Switzerland. Siemens-Elema had been added in Scandinavia, and Mitsui in Japan.

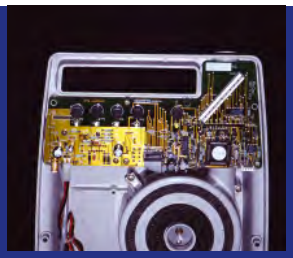
Disappointment came from the USA where the distribution agreement made as recently as October 1990 was not living up to expectations. The problem was fundamental. Medtronic's strategy for selling in the USA was to by-pass the close-knit home healthcare dealers, and sell direct to the patient. The result was not good. A final attempt to return to the home healthcare dealers was unsuccessful. By April 1992, the agreement with Medtronic was dissolved, inventory was repurchased, and four of Medtronic's sales people were taken over to sell direct from ResCare. Medtronic became a passive investor in ResCare, through 200,000 options granted for US$8, exercisable December 1995. In the end, Medtronic did better from investment than from marketing product.

Many years were to pass before the potentially huge USA market became profitable.

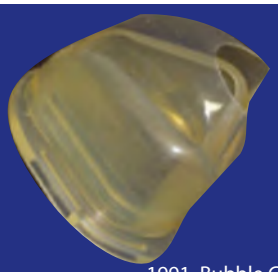
In November 1992 the value of patents was effectively demonstrated. Respironics had begun selling in Australia through an agent, Anaesthetic Supplies Pty Ltd. Their products were seen to be clearly infringing Colin Sullivan's original patent, then owned by ResCare. An action claiming infringement was brought against Anaesthetic Supplies. It came before the court from June to August. The carefully reasoned judgment[xxxvi] found in ResCare's favour. The only change required by the Judge was that "snoring" be removed from the Claims.

Respironics responded by lodging an appeal.

Doubling of sales each year puts stresses on management and accommodation. ResCare had already made one move from its former BCMR offices, into larger offices at Lyon Park Road, North Ryde (demolished in 2005). With production growing quicker than infrastructure, it became necessary to move to more spacious premises with workshop space in addition to offices. The solution came through renting part of a building at 82 Waterloo Rd, North Ryde (demolished in 2006) that included open warehouse space in addition to offices. Two floors of workshops and offices were built within part of the open warehouse. Eventually as other tenants moved on, and ResCare's needs grew, the whole building was rented and converted to meet ResCare's requirements. The move in 1992 gave 1400 m^2 of space that was sufficient to increase manufacture to 1000 units per month. Capacity for mask production was quadrupled.



Delay timer in S3 Flow generator



1991 Bubble Cushion Series 2

1993 Bubble Cushion Series3

During 1992, ResCare continued to come to the notice of the business community in Australia and internationally. ResCare was acknowledged for Achievement and Excellence in New South Wales Small Business, and was a finalist in the Australian Exporter of the Year Award.

The move away from an independent distributor in the USA to a wholly owned ResCare subsidiary proved to be of critical importance for the future. Revenues in fiscal year ending 30 Jun 1993 increased 143% over the previous corresponding period, to A$11.8 million. If ResCare were ever to be a significant global company, it would be on exports, of which the USA would be expected to lead. The Federal Government through its Austrade division was again of assistance by providing a A$1.1 million long-term loan at favourable interest rates to assist exports to the USA. In 1993 exports grew comfortably to 77% of production, of which the USA accounted for 50%. The trend of an increasing proportion of production being exported, with USA taking 50% of exports was well established and continued for more than a decade. ResCare was doing well in Germany through Priess, a good start had been made in Sweden, and sales had begun slowly in Belgium, France, Holland, and Spain. Although an increasing proportion of production was going to exports, the Australian market was not neglected. ResCare's distributor, Medical Gases, had set up three private clinics and was filling flow generator requirements elsewhere throughout the country.

The Australian market had been useful in the first few years of the Company's existence by providing sales sufficient to demonstrate that here was a viable business. The resulting cash flow established facilities to grow the market.

During 1993, technology continued to improve. The Bubble Cushion, which in its original Series 2 form retained the firm face contact of the Series 1 cushion along with the thin bubble film, was modified. Introduced in January 1993, as Series 3, the firm component was abandoned as a separate structure. Instead, the base of the bubble film was thickened for attachment to the mask frame. The mode of operation between the Series 1 mask and Series 3 bubble was fundamentally different. In Series 1, the part contacting the face made the seal over a narrow area with the facial skin being deformed slightly by pressure from the cushion material. With the Bubble series, the thin membrane spread over a larger skin area without deforming the skin. With head movement, the Bubble film maintained leak-proof skin contact by rolling during a considerable degree of movement.

Headgear supporting the mask looks simple. It is but a few straps holding the mask close to the face. Finalising the design and materials of construction required a research project of significant dimensions. There had to be no place where straps cross each other to result in an uneven surface. Prolonged contact with the skin necessitated a minimum of irritation and total freedom of allergens. For almost any conceivable material there will be someone who demonstrates an allergy. Concerns were frequently raised by customers who associated highly allergenic rubber vulcanising chemicals with totally nonallergenic silicone and other plastic materials.

Sullivan III 1993

Passover Humidifier

Fisher & Payel Heated Humidifier

After many trials a creation of coloured cotton fabric designed to provide stable support to the mask frame was named ResCap.

Later a small change in materials in the mask may have helped maintain high sales numbers. Originally, the silicone elastomer of the cushion had effective mechanical properties, while being opaque. A much better cosmetic effect came from use of a silicone as clear as glass.

Above all other considerations, achieving an airtight fit with the mask is the essential feature for success with CPAP. Others had tried with such cumbersome contrivances as a stiff gel in plastic wrap to be moulded to the contours of the face each night. Another had a flap of flat plastic film along the inner edge of a face-deforming mask. Waving like a flag in a breeze it did not fill the maker's expectations of maintaining the essential seal during head movement. In contrast the delicate, light film of Bubble *Universalmaske* exceeded all expectations to reinforce ResCare's technical superiority. As market volume and market share grew, mask designers could now rest on their laurels. But they did not.

Philip Kwok Industrial Designer

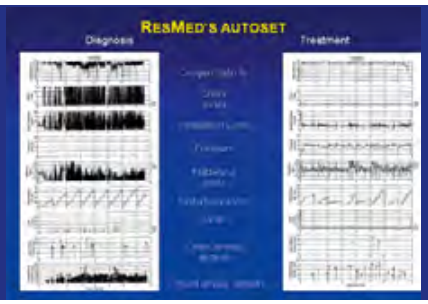
The effect of success stimulated Philip Kwok, with help from Ken Hely and Bob Styles to greater efforts toward perfection.

They took inspiration from earlier successful masks to design a firm silicone cushion that conformed to facial contours, and added an internal narrow film to make the final seal. A new family of masks carrying the Mirage brand was born.

Flow generator design took a further step forward with release in May 1993 of the Sullivan III. This had microprocessor control that allowed self-diagnosis, and pressure adjustment without need for a screwdriver. To satisfy German requirements, a pressure transducer was incorporated to maintain pressure in the mask for Constant CPAP.

During winter in cold climates, the flow of very dry air into the nose causes irritation of the nasal membranes. This is aggravated by mouth leaks that allow excessive airflow through the nose in one direction. Humidification of the airflow from the pressure generator can minimise or usually eliminate damage. Passive humidification with inspiratory and expiratory air passing through a sponge impregnated with calcium chloride was tried, but it was not sufficiently effective to become a standard method. A cold water passover humidifier with an extended turbulent airflow path was designed to fit under the current flow generators. After a slow development, a heated CPAP humidifier became available from Fisher & Paykel. ResCare had exclusive rights to distribution in North America. It was the result of collaboration between engineers from ResCare and F&P, and was supplied to ResCare under contract. The collaboration had ramifications that became apparent years later[xxxvii].

Dr Michael Berthon-Jones



First AutoSet Patient (1993)

The Humidaire series was introduced in 1997.

Detection of snoring had proven neither consistent nor practical for detecting an impending apnea. With snore detection, sensitivity was reduced by competing sounds from the motor, fan, and mask vents. A fundamental flaw was that when the applied pressure was sufficient to just eliminate snoring, there was still airway narrowing and difficulty in breathing. Thus detection of snoring tended to under-treat. The limited success achieved did validate the concept and stimulated interest in the search for more sensitive methods of apnea prediction.

In an attempt to overcome these difficulties, Chris Lynch with Colin Sullivan added breathing rate and inhaled airflow to the detection method for US patent 5,245,995. Although this marked an improvement in sensitivity and effectiveness, the technology was rendered obsolete before the patent issued in September 1993.

In 1992, in Colin Sullivan's sleep laboratory, Michael Berthon-Jones[xxxviii] noted changes in the respiratory airflow versus time chart. As the airway began to reduce in size a characteristic flattening of the smooth sinusoidal curve of normal breathing appeared before clinical signs were apparent. Berthon-Jones developed an algorithm that compared the shape of the airflow curve of the current breath with the average of previous breaths. At the commencement of flattening, air pressure was gradually increased to a level at which the shape returned to that of normal breathing. The pressure was then reduced to a low maintenance level.

This was a novel finding that served as the basis for a sensitive control of pressure to the airway that became the basis of AutoSet[xxxix]. It was later introduced into some competing devices.

The growing realisation of the importance of OSA attracted medical research scientists in increasing numbers to study its pathophysiology, and its comorbidities and consequences. It is inevitable that there is a lengthy time lapse between initiation of a clinical research project and the appearance of results in print. To keep abreast of academic research developments, their clinical consequences, and their impact on ResCare's operations, a Medical Advisory Board (MAB) was formed. It is a tribute to the status that this small new company had acquired in the research fraternity that the MAB was led by the inventor of nasal CPAP, Colin Sullivan. Support came from Professor WC Dement, "Father of Sleep Medicine" and founding member of the Stanford Sleep Disorders Clinic. Other members were Dr Neil Douglas from the University of Edinburgh and the Scottish National Sleep Laboratory, Dr Ralph Pascualy, Director of a medical center in Seattle, and Professor Clifford Zwillich, of Pennsylvania State University. These last three had extensive clinical experience. The Medical Advisory Board was to meet twice each year to discuss medical advances with senior staff, and assist in clinical applications and design of equipment.

Academics were not the only people becoming interested in OSA. In addition to Respironics in the USA, in fiscal 1994, two companies had begun selling CPAPs in Germany.

Unquestionably, ResCare had global ambitions.

VPAP 1994

AutoSet Clinical 1994

It might survive in Australia as a niche player in a world market. If it were to become a substantial company, it had to export in quantity. It was apparent that for the time being, Europe and the USA would provide the biggest opportunities. In the absence of reliable prevalence data, the potential size could only be guessed at. Whatever the size, with very limited resources, it was going to be hard to grow organically. In particular, the key North American market was being serviced by Respironics, already an established company. To compete would be extremely difficult, with every conceivable factor weighing against ResCare. Some uncertainty had to be expected while Sullivan's basic patent was before the court of appeal.

By now, 12 years had passed since Sullivan's successful demonstration of CPAP treatment and there was no acceptable knowledge of community prevalence. Finally, a group led by Terry Young[xl] at the University of Wisconsin produced (43) reliable numbers on the prevalence of OSA[xli] in an adult working community. The prevalence of 4% females and 9% males having OSA at a level that needed treatment was higher than prior expectations. The cost of OSA to health[xlii] now had to be acknowledged as similar to that of the well-publicised health costs of tobacco, as noted by Eliot Phillipson (20).

The length of time taken to establish that a sizable market existed seemed unduly long. However, to get data that will stand up to scrutiny takes extensive resources and rare expertise, with a substantial source of financial support. The delay was probably to ResCare's advantage. Had an established large company realised the potential, they could have started with resources that ResCare in its formative years could not have matched. By 1993, the global market was effectively divided between two companies - Respironics and ResCare. This put a significant barrier to entry of further contestants. Other companies were becoming interested but at this stage were no more than niche players.

In fiscal year ending 30 June 1994, sales were US$13.75million, an 80% increase over the previous years, with the USA providing 50% of revenue. Peter Farrell, as Chairman of the Board, was delighted that revenues and profits had provided a compound annual growth rate of about 100% for each of the 5 years since the company was formed. He cautioned that maintaining such a growth rate in future would be "challenging". During the 1994 fiscal year, Australian sales were down to 20% of the total, with the USA again accounting for more than 50% of total revenues. With the growing importance of the global market, and the US market in particular, ResCare Inc was registered in Delaware as a joint US/Australian company. Additional funds for growth were obtained through sale of 100,000 shares to Nomura/Jafco.

Flow generators were being produced at the rate of 2,500 per month, with production working 2 shifts. Refinement of sensor technology allowed development and introduction of features giving more machine control for greater patient convenience.

In 1993, Dr John Brydon[xliii] brought his considerable skills in signal processing and biomedical engineering to the ResCare research group. With Michel Calluaud he developed a system where airflow automatically stopped when the mask was removed from the face and automatically started when the mask was replaced. The rapid drop of pressure when the mask

was removed from the face signalled the motor to stop. When the mask was replaced, sensing the increased pressure from breathing signalled the motor to restore the therapeutic pressure (US Patent 6,240,921). SmartStart™ was introduced in September 1994.

Respironics introduced their BIPAP in 1989[xliv]. The rationale was that compliance was adversely affected for those people who found breathing out against the constant pressure to be too uncomfortable. In June 1994 ResMed released VPAP for delivery of set variable pressure and AutoSet Clinical. AutoSet Portable arrived in February 1995.

At the beginning of 1993, ResMed's commercial position in the USA looked extremely strong. The US version of Sullivan's original CPAP patent (US 4,944,310) had issued in July 1990. Its purpose was to give a monopoly on use of CPAP. During the year, three patents were due to issue, protecting the delay timer (US 5,199,424, issued 6 April 1993), Bubble Mask (US 5,243,971, issued 14 Sep 1993) and Auto Feedback, that is, AutoSet functionality (5,245,995, issued 21 September 1993). As they issued, negotiations commenced with many companies to exploit these patents.

Most companies procrastinated. Puritan Bennett agreed to pay royalties on the delay timer patent. Respironics had a better idea. They (McGinnis personal communication to Dr Farrell) volunteered that since Respironics had the market, and ResCare had the technology, a merged company would benefit both parties. The concept was gladly accepted for examination. It seemed a good idea at the time.

Respironics, as the bigger party, began its due diligence to establish the worth of each company. Continuously for nine months teams of six or more people from Respironics' finance and technical departments came and went, taking notes, copying documents, examining patent applications, interviewing staff, getting every minute detail of the technology under development, and the state of the finances. All this was done under the security of a secrecy agreement, believed at the time to be a legally binding document.

By the end of calendar 1993, the comforting protection of the patents began to crumble. Three Judges of the Australian Federal Court handed down a judgement upholding Respironics' appeal against the validity of Sullivan's basic patent intended to cover CPAP use. The patent was revoked[xlv] in its entirety. Finality was not reached until 14 October 1994, when all avenues of appeal were exhausted. ResCare no longer had any protection in Australia against a competitor introducing nasal CPAP. The rest-of-world would certainly follow suit. Adding further injury was the awarding of legal costs of US$290,000 against ResCare. Worse was to come. A few hours before signing the proposed agreement for a merger of Respironics and ResMed, Respironics withdrew (ResCare Annual Report 1993-4), and declined to licence any patent.

ResMed was then left with no option but to initiate an action alleging infringement of ResMed's three surviving patents. The legal drama had begun, and would continue for years, following set-piece routines developed over many legal lifetimes. Respironics denied infringement, and asserted that all the patents were invalid and unenforcable. By May 1995 in a separate action, Respironics made a statement of claim alleging ResMed had engaged in unfair trade practices in Australia, and claiming A$730,000 in lost profit from sales. The implication was that they had been denied the Australian market through a faulty, revoked, patent.

To this time, all legal actions and preparation of intellectual property filings were done through independent companies, with no professional legal contact within ResMed. The complete staff

list worldwide, including consultants, had less than 100 members. With impending complex litigation in two countries and patentable technology being produced at an increasing rate, there was need for an experienced attorney in-house. Mark Abourizk[xlvi] was taken on board. He has been kept busy ever since.

The year 1995 was climactic in ResCare's history.

On the one hand, business was doing well. Coming on to the market was a stream of improved and new products with the capacity to diagnose and treat disordered breathing. AutoSet Portable had arrived, AutoSet CS was in the pipeline, along with a series of improved CPAPs carrying the Sullivan brand. The size of the market was growing as OSA became linked to a broader range of comorbidities, and education spread to more countries. Economic studies were highlighting the dollar cost of sleep disorders that Phillipson had claimed were equal to those caused by tobacco. Analysts from the broking house William Blair were estimating the prevalence of OSA in the US market to be in the order of 6 million. Revenues of US$23.5 million that were expected during fiscal year 1995 represented a 69% growth over the previous year. Again the USA growth rate of 92% exceeded the very good 62% growth in Europe. What was more significant was that when abnormals were taken out, net income showed an 85% growth year on year.

Against this, there was litigation that at best would be expensive, and at worst, prolonged and debilitating. The intellectual property that formed the foundation of the company was diminished, with the remainder in question. Competition was growing from established companies in USA and Europe.

The solution was to go international more aggressively. ResCare changed its name to ResMed, simply because its name of Australian origin was already registered in the USA.

On 2 June 1995, ResMed joined the ranks of leading world technology companies.

It listed on the NASDAQ stock exchange.

Epilogue

"SDB is our long suit, our short suit, in fact our only suit"

Peter C Farrell

ResMed's 1995 float was a success, with 3,000,000 shares issued initially at US$11, rapidly rising to US$13 to raise US$25 million. Underwriters were broking houses Robertson Stephens, William Blair and Nomura Securities. The P/E obtained was about 20. This compared with a P/E of about 10 suggested by the less experienced Australian underwriters. More than a decade later in 2007, the actual P/E had risen to around 40. One reason for the rise was that the USA prevalence of OSA as reckoned by William Blair to be about 6 million, was soon found to be more like 20 million.

William Blair remains a major stakeholder and trader. Robertson Stephens did not survive the dotcom crash. ResMed survived the crash better than the NASDAQ 100 index which still struggles to recover its highs of the tech bubble. The only major hiccup to the share price relative to the Market in 12 years came from a media beatup in 2001-2 of the entry of a competitor claiming superiority with a novel mask. ResMed's growth in revenue and profits continued unabated, with the share price soon recovering its upward momentum.

One reason for the continuing success of the company has been its innovative successes in product development. Without exception the functional products that laid the foundations of the company in 1995, have all been continuously improved over time. Each innovation has been more successful than its predecessors. It is ironic that in 2004 the most recent and most successful mask innovation returned to closely comply with Sullivan's original concept of "up your nose with a rubber hose". Now the tubes are not glued in the nares, they are soft silicone elastomer "pillows" held in place by a simple headgear.

As such they would almost certainly have overcome the objections of the Appeal Judges to Sullivan's original patent. Had that happened … but it is better not to speculate on past events.

The actions between Respironics and ResMed continued indecisively until 5 September 2003 when "ResMed Inc and Respironics, Inc announced that they had settled all patent infringement lawsuits pending between them. This settlement resolves all matters relating to the 1995 action by ResMed, and the corresponding claims and counterclaims by Respironics … and all matters relating to the 2002 action by ResMed." It had indeed been a prolonged and expensive diversion.

There has been notable stability in the company Board since the IPO in 1995. Dr Farrell has remained President and Dr Chris Roberts has been a member continuously since 1992. Non-Executive Directors Dr Gary Pace, Michael Quinn, and Donagh McCarthy have continued to bring their combined scientific and commercial experience to benefit the Company continuously since 1994.

With 17 years of experience behind it, ResMed can take pride in its achievements. By providing an effective and commercially successful treatment to one of the commonest and medically most significant disorders of mankind it has opened up a huge area of medical awareness, and brought good health to sufferers already numbered in their millions. The confidence of investors in the Company's future has been rewarded.

ResMed Corp. - Ex. 1030
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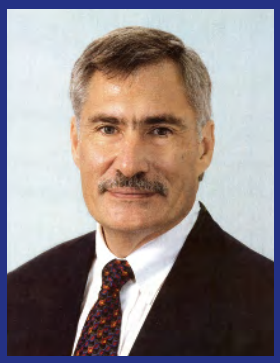
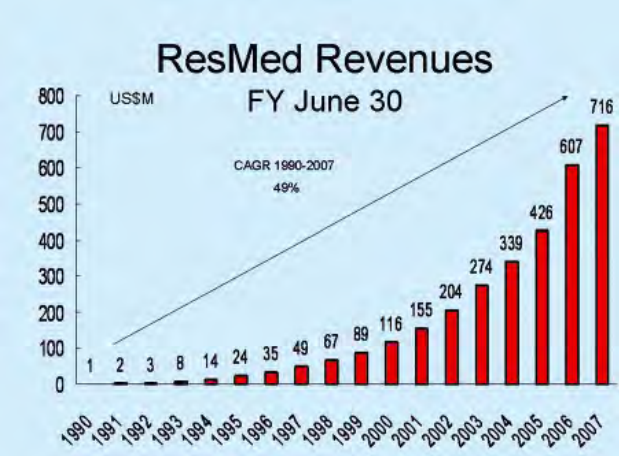


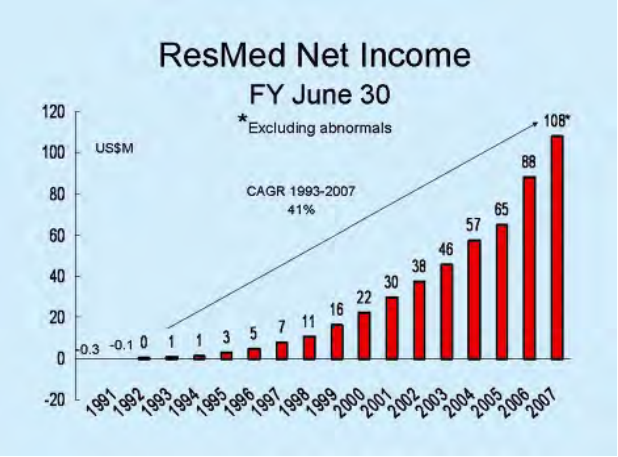
Dr Gary Pace 1995

Michael Quinn

Donagh McCarthy

ResMed share price compared with NASDAQ composite index





APPENDIXES

TREATMENT of OSA

One of the factors limiting progress in unravelling the importance of sleep disordered breathing to the community was the absence of a widely acceptable and successful treatment of OSA. Treatment would be useful to ease the disease burden on the sufferer. To the research scientist it was essential to establish whether OSA was the cause, rather than the effect, of an observed association with a comorbidity.

On the pathophysiology of OSA, an interesting account is given (31) on how, during Hominid evolution to an upright stance to achieve a bipedal form of locomotion, the face has retracted under the cranium, enlarged by superior brain power. The adult lower jaw cannot then fully accommodate the tongue, as is achieved by all quadrupeds. Instead, the tongue base has been forced back and curved down to form the front wall of the breathing tube at the back of the mouth – the oropharynx[xlvii]. No skeletal structure evolved to compensate for this insult to airway space, form, and function. Instead, a dozen or so dilator muscles have the responsibility of maintaining a free passage of air to the lungs by holding the airway open. At night all muscles relax to recover from the day's activities. Dilator muscles are not totally free from this requirement, though they can not resist reducing the strength of their action. The result is a tendency for the airway to be less strongly supported. The worst effect is to allow the tongue, now the anterior wall of the oropharynx, to drift into the oropharynx. This causes a reduction of area of the airflow pathway. The effect is worsened when lying on the back (supine), with gravity adding to airway reduction or by pre-bedtime alcohol that reduces the automatic function of all the muscles. Infants are born at an earlier evolutionary state where this inconvenience has not developed. They have the quaint capacity to suckle and swallow while obligatorily breathing through their nose. Dr Terence Davidson has considered how the acquisition of speech is associated with OSA (32, 33).

Earliest observers knew that the blockage during obstructive apneas was somewhere in the upper airway. With OSA, respiratory muscles of the diaphragm and chest can be seen to be functioning because of visible movement of the chest and abdomen. Yet no air is entering the lungs. Remmers had shown that the blockage was as high as the pharynx (19). The solution then was obvious - tracheotomy. Simply cut a hole in the trachea below the pharynx, the blockage is by-passed, and the patient is cured.

Tracheotomy for treating OSA was first reported from Germany by Kuhlo et al (23) in 1969 and was used by Lugaresi et al (25) in Italy in 1970. The Stanford Clinic adopted it widely and successfully. Guilleminault could say that by 1980 the Stanford Clinic had very successfully treated 50 patients.

In the absence of an alternative, we should not underestimate the value of tracheotomy. The best physicians could offer nothing better. Sullivan, in 1980, noted that the results of tracheotomy were dramatic. Excessive daytime sleepiness was abolished within days, and life threatening arrhythmias or cor pulmonale improved rapidly. Dement could report (16) that a person near death from OSA given a tracheotomy in 1974, was alive and well in 1998. Tracheotomy worked in the 1970s, and even now it can be justified in extreme emergencies, or with people incapable of handling more complex or intellectually demanding alternatives.

To a surgeon, the procedure is simple, the results effective. The hole can be covered during the day and left open at night to allow normal breathing. Guilleminault qualified his enthusiasm for the operation with the comment that "it should be reserved for patients with severely disabling conditions, and with life-threatening cardiovascular events". There is no record of patients' opinions. It may be safely assumed that a less invasive treatment would be preferred if it were available.

The success of tracheotomy in curing symptoms stimulated search for less destructive methods.

Other surgical techniques were developed to prevent snoring and apnea. To prevent snoring, palatal tissue had to be stiffened or reduced in size. To prevent apneas, the oropharynx had to be enlarged, or prevented from diminishing during sleep. Enlargement of the oropharyngeal area could be achieved by removal of tissue or by adjusting the facial bone structure. The earliest method was uvulopalatopharyngoplasty or UPPP (26), introduced in the same year as noninvasive CPAP. With UPPP, the soft palate is shortened by scalpel, with loss of the uvula, an organ in its own right (52). A modification from China saves the uvula (27). Scarring by laser could stiffen the palate to reduce the vibration that was the cause of snoring noise. The palate may also be stiffened with inserted plastic strips. Removal of tissue from the palate or tongue-base by laser ablation is designed to enlarge the oropharyngeal cavity. The most complex surgery involves severing mandible and/or the maxilla, and advancing the front part to enlarge the oral cavity.

There is no doubt that surgery is necessary to correct abnormal physical anatomy. A fundamental difficulty with surgical methods for treating the most common OSA is that they do not address the tone of the dilator muscles when they are deficient in holding the airway open. Side effects can include voice changes, regurgitation of food through the nose, and regrowth of tissue. Effectiveness of surgical methods in the absence of abnormalities is usually not comparable with results from CPAP.

The literature on surgical methods gives an inflated view of their effectiveness, as surgeons use less stringent criteria of effectiveness than physicians with noninvasive methods. Only recently has a suggestion been made in the medical literature for a more meaningful description of surgical outcomes in terms of clinical efficacy (58).

Cochrane reviewers (28) put a perspective on the situation by saying "the available evidence … does not currently support the widespread use of surgery in people with mild to moderate daytime symptoms associated with sleep apnoea". That is a correct assessment.

Oral appliances are the most widely used and least invasive methods of enlarging the oropharyngeal cavity. Oral appliances were originally proposed to prevent snoring. Most are now promoted to include obstructive apneas.

One type does this by pulling the tongue forward. The most popular are mandibular advancement devices (MAD) made by dental technicians. Cochrane reviewers say (29) "Although CPAP was clearly more effective at reducing the disruption to sleep, some people with OSAH may prefer using them (oral appliances) if they are found to be tolerable and more convenient than CPAP. When an active OA was compared with an inactive OA, there were improvements in daytime sleepiness and apnoea/hypopnoea severity. OA may be more effective than corrective upper airway surgery".

There have been numerous attempts to find a drug therapy for OSA, so far with little success (30).
Electrical stimulus of nerves to the dilator muscles is experimental.

CONSEQUENCES and COMORBIDITIES of OSA
The medical consequences of obstructive sleep apnea may be considered to arise from five primary causes. There is a complex interaction between these that is still being resolved. The following discussion is a simplification based on what is known.

The most obvious symptoms arise from interruption of sleep. It is easy to see how this results in excessive daytime sleepiness and reduced quality of life. More serious are the demonstrated deficits in cognition and increased accident rate.

Less obvious may be disturbance of circadian rhythm with detrimental effects on production of growth hormone and testosterone. These are hormones that are not produced continually in response to a demand, but are dependent on sound and regular sleep. Consequences of male sexual dysfunction has been demonstrated with OSA subjects.

Growth hormone is essential for health in all age groups. Children with OSA through tonsillar hypertrophy have been shown to suffer growth inhibition in addition to cognitive deficits. With adults the consequence is more likely to be in quality of life.

Intrathoracic pressure changes occur in the cycle of apnea followed by recovery of breathing. During breathing the diaphragm acts as a piston to draw air into the lungs. The struggle of the muscles of respiration to draw air into the lungs against a closed upper airway during an apnea causes a significant reduced pressure (partial vacuum) in the thorax. This affects two other structures that share thoracic space with the lungs. These are the esophagus and the heart.

The esophagus is a tube taking anything swallowed from the mouth to the highly acid stomach. A weak sphincter prevents backflow of stomach contents into the esophagus. A functional defect allowing backflow results in gastroesophageal reflux (GER), with heart burn and more serious consequences long-term. The process is enhanced by OSA-induced pressure swings in the thorax.

The heart has two sets of chambers. Thin-walled atria collect blood from the body or the lungs, measure the volume, and with a weak pumping action pass the blood to the ventricles with their strong muscular walls for circulation to the body and lungs. Reduced pressure in the thorax affects both atria and ventricles.

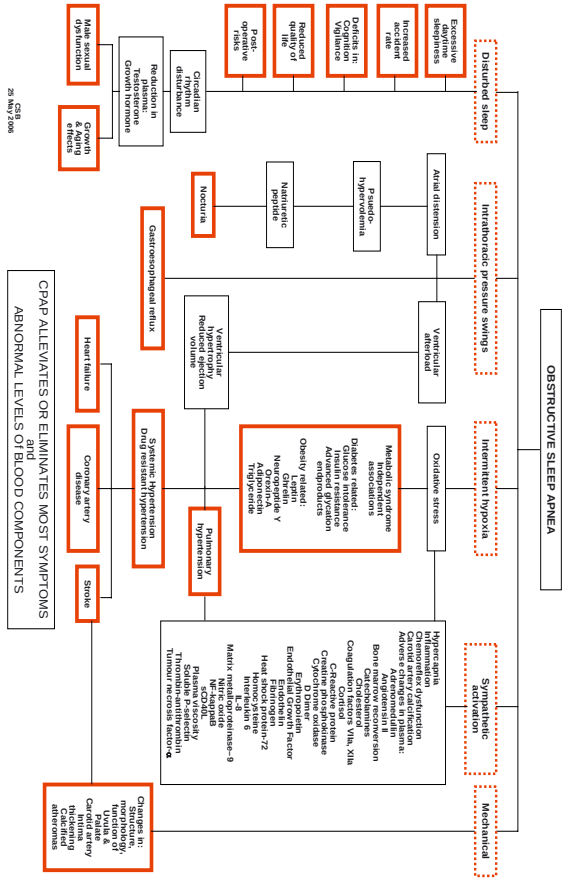
Soft-walled atria are distended by the suction. Normally, atria are distended only when blood has absorbed more water than is needed. Atria then produce a hormone messenger, called natriuretic hormone, that causes kidneys to reduce water content by producing urine. Suction during apnea has the same effect to cause excessive urination in both adults and children.

The left ventricle has the job of pumping blood around the body. Reduced pressure makes it work harder, causing the muscle to grow stronger and bigger, which reduces the volume being ejected on each stroke, which causes the heart to pump harder, and so on, to contribute to congestive heart failure.

The strain put on the body's resources by recurring apneas and arousals cause enormous stress. During apnea the blood and organ's reserves of oxygen are depleted, causing generalised hypoxia. On arousal the heart which has slowed to conserve oxygen during apnea frantically has a surge of rate and activity. There is over excitation of the sympathetic nervous system.

Much of this is shown by production of inflammatory factors, some score of which have been identified. Metabolic disorders arising are glucose intolerance and insulin resistance. Sensitivity to hormones that regulate appetite and weight is diminished. Worst is hypertension, for which OSA is the most serious known cause. OSA is highly prevalent with diabetes, congestive heart failure, coronary artery disease, and stroke.

Snoring that occurs with apnea has demonstrated mechanical consequences. The function and morphology of the palate and uvula suffer through continuous vibration. Close to the vibrating palate lie the carotid arteries. With apneics, there is a demonstrated tendency to a buildup of calcified atheromas. It is postulated that the vibration produced by snoring could shake loose pieces of atheroma to induce ischemic stroke.



Awards: ResMed Group

2006

Forbes Magagine's 200 Best Small Companies in America (#86). For the 10th consecutive year- a record for a technology company
Engineering Excellence Australian Award (Australian Institution of Engineers)
Australian Exporter of the Year
NSW Premier's Exporter of The Year
New South Wales Exporter of the Year - Advanced Large Manufacturer
06 Engineering Excellence – Category R&D from Engineers Australia
APICS NSW Company of the Year http://www.apics.org.au/chapters/nsw/News/
Australian Design Award
Western Sydney Industry Award – Most Outstanding Large Business
Manufacturer of the Year from UK Association for Respiratory Technology & Physiology

2005

NSW Premier's Exporter of the Year (Large Advanced Manufacturer)
Forbes Magazine's 200 Best Small Companies in America (#51)
Frost & Sullivan Sleep Therapy Product Quality Leadership of the Year Award
Frost & Sullivan Patient Monitoring Company of the Year Award
Business Week's 100 Hot Growth companies (#54)

2004

NSW Premier's Exporter of the Year (Large Advanced Manufacturer)
Forbes Magazine's 200 Best Small Companies in America (#29)
Business Week magazine's 100 hottest-growing small companies (#82)
Fortune magazine's 100 Fastest Growing Small Business Companies (#89)

2003

Forbes Magazine's 200 Best Small Companies in America (#35)
Business Week magazine's 100 hottest-growing small companies (#32)
Investor's Business Daily's "Top 100" Companies in America (#89)

2002

Australian Exporter of the Year
NSW Premier's Exporter of the Year
Forbes Magazine's 200 Best Small Companies in America (#18)
American Association for Respiratory Care's Zenith Award

2001

Forbes Magazine's 200 Best Small Companies in America (#24)
Fortune magazine's 100 Fastest Growing Small Business Companies (#30)
Business Week magazine's 100 hottest-growing small companies (#31)
Top performing company in the Investor's Business Daily's "medical products" category

2000	Australian Technology Awards : Excellence in Development of Biotechnology, Pharmaceutical Technology and Medical Instrumentation and Excellence in Globalization of Technology. Forbes Magazine's 200 Best Small Companies in America (#34) Fortune magazine's 100 Fastest Growing Small Business Companies Business Week magazine's 100 hottest-growing small companies (#58)
1999	Forbes Magazine's 200 Best Small Companies in America (#27, including being one of the "12 to watch" and "Supercharged 10") Fortune magazine's 100 fastest growing companies Business Week magazine's 100 hottest-growing small companies (#67)
1998	Forbes Magazine's 200 Best Small Companies in America (#63) Premier's NSW Exporter of the Year NSW Exporter of the Year (Large Advanced Manufacturer Award, Australian Institute of Export) Deloitte and Touche's Technology Fast 50 for the California Orange Coast
1997	Deloitte and Touche's Technology Fast 500 Forbes Magazine's 200 Best Small Companies in America (#172) Awarded $2 million competitive AusIndustry's R&D START Program grant Award, Australian Venture Capital Awards
1995	NSW Exporter of the Year Award (Australian Institute of Export)
1992	Finalist, Exporter of the Year Awards (Austrade) Finalist, Awards for Achievement and Excellence in NSW Small Business
1991	International Business Achievement Award (Austrade) Australian Government National Procurement Development Grant of $375k Australian Chamber of Manufacturers Small Business Achievement Award
1990	Austrade International Business Development Grant of $110k
1989	Australian Government R&D Grant for $150k

Awards: Dr Peter Farrell

2007	Ian Clunies Ross Award of the Australian Academy of Technological Sciences and Engineering
2006	University of NSW Alumni Award in Business & Commerce Honorary Fellow of the Australian Institution of Engineers
2005	Ernst & Young National Entrepreneur of the Year for Health Sciences for America Warren Centre Hero of Innovation University Sydney
2004	Member of the Order of Australia
2002	Australian Export Hero
2001	Ernst & Young's Australian Entrepreneur of the Year
2000	KL Sutherland Memorial Medal of the Australian Academy of Technological Sciences and Engineering for Application of science for the benefit of the community (shared with Colin Sullivan) AT&T International Business Leadership Award (San Diego World Trade Center) Distinguished graduate Speaker of the University of Sydney
1998	Ernst & Young San Diego Entrepreneur of the Year in Health Sciences
1997	David Dewhurst Award for significant contributions to biomedical engineering (Australian Institution of Engineers)
1994	National Engineer of the Year (Australian Institution of Engineers)

ResMed Patents issuing prior to IPO

1981 Apr	US 4944310	Sullivan's CPAP patent	CE Sullivan
1987 Jun	US 5199424	Delay timer	CE Sullivan, CE Lynch
1987 Jun	US 5245995	Auto feedback	CE Sullivan, CE Lynch
1990 May	US 5243971	Bubble mask (Licensed)	CE Sullivan, J Bruderer
1991 Dec	Not yet issued	Small bore	CE Sullivan, CE Lynch, M Berthon-Jones, & M Calluaud
1994 Jun	US 5560354	Nose and mouth mask	CE Lynch, M Berthon-Jones, M Calluaud, K Hely
1994 Nov	US 5704345	AutoSet	M Berthon-Jones
1994 Nov	US 6240921	Smart Start	J Brydon, M Calluaud
1994 Dec	US 5740795	Flow estimation	J Brydon

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Timeline of ResMed product introduction

2007	September	S8 II
	May	Quattro Mask
	May	Liberty Mask
	April	VPAP Malibu
	March	C-Series Tango
2006	September	Swift II
	June	1,000,000 Swift masks made
	February	Meridian
2005	June	Ultra Mirage II
	May	SAIME acquired
	April	S8
	March	Hospital Full Face
	March	Hospital Nasal mask
2004	October	Mirage Kidsta
	October	Mirage Swift
	August	VPAP IIISTA
	April	ApneaLink (MicroMesam)
2003	October	Mirage Activa / AutoSet CS2
	September	AutoSet Respond
	July	Ultra Mirage Full Face
	April	VPAP III
	January	ResLink
2002	November	S7 Lightweight
	October	Mirage Vista
	August	Full Face Series III NV
	August	Ultra Mirage NV
	November	S7 Elite
	May	SMI acquired
	April	Papillon (in Germany)
2001	October	Full Face Series II
	October	AutoSet Spirit
	February	MAP acquired
2000	November	Embletta
	October	Mirage NV Full Face / AutoSet CS
	June	Ultra Mirage
	June	S6
1999	October	Embla
	September	ResControl
	June	Mirage Full Face
	March	AutoSet T

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1998	November	VPAP MAX
	August	VPAP II ST A
1997	December	Humidaire humidifier
	August	Mirage
	June	AutoSet Portable II Plus
1996	November	Nose and mouth mask
	November	ResCap II
	June	Purchase of French distributor
	April	VPAP II ST
	March	Comfort
	March	VPAP II
	February	Purchase of Priess Medizintechnik
1995	July	Sullivan V
	April	Sullivan Alert
	March	Sullivan Pediatric
	February	AutoSet Portable
1994	October	Sullivan IV
	August	Infant mask system
	June	VPAP, AutoSet Clinical
1993	October	Constant CPAP
	September	ResCap
	May	Sullivan III
	January	Bubble Cushion (series 3)
1992	April	Medtronic distribution agreement relinquished
1991	April	APD2
	February	Bubble Cushion (series 2)
1990	October	Medtronic / ResCare USA distribution and equity agreement
1989	September	ResCare releases APD1
	August	ResCare management buy out of Baxter's interest in CPAP
1988	September	Baxter releases R2, Standard mask
1987	December	Baxter Centre for Medical Research purchase Sullivan's patents and technology
1981		Sullivan invents CPAP treatment for OSA

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References

1. Kryger MH: *Sleep Apnea From the needles of Dionysius to continuous positive airway pressure;* Arch Intern Med, 1983 143 2301-3
2. Levie P: *Nothing new under the moon, Historical accounts of sleep apnea syndrome*, Arch Intern Med 1984, 144, 2025-8
3. KielyJL & McNicholas WT: *Overview and historical aspects of breathing disorders during sleep*, Eur Respir Mon, 1988, 10, 1-8
4. Michalopoulos A, Tzelepis G, & Geroulanos S: *Morbid obesity and hypersomnolence in several members of an ancient royal family*, Thorax, 2003, 58, 281-2
5. Polkey MI, Morrell MJ, & Simonds AK: *Apnea and history*, Chest 125, (4) 1587
6. Sotos JG: Taft and Pickwick, *Sleep apnea in the white House*, Chest 2003, 124: 1133-1142
7. Margolis ML: *Brahms' lullaby revisited*, Chest 2000; 118:210-213 and subsequent correspondence
8. Wadd W: *Cursory remarks on corpulence; or Obesity considered as a disease: With critical examination of ancient and modern Opinions relative to its causes and cure* ed 3. London, Gallow Medical Bookseller 1822 – original not seen
9. Broadbent WH: *Cheyne-Stokes respiration in cerebral haemorrhage* Lancet 1877 1 307-9
10. Dement WC: *History of sleep medicine* 2005 Neurologic Clinics 23 945-965
11. Burwell CS, Robin ED, Whaley, & Bickelman AG: *Extreme obesity associated with alveolar hypoventilation: a Pickwickian syndrome* Am J Med 1956 21 811-18 original not seen
12. Gastaut H, Tassinari C, Duron B: *Etudé polygraphique des manifestations episodiques du syndrome de Pickwick* Rev Neurol 1965 112 568-579
13 Jung R & Kuhlo W: *Neurophysiological studies of abnormal night sleep and the Pickwickian syndrome* 1965 Progress in Brain Research ;18:140-59
14. Duron B, Tassinari C, Laval P, & Gastaut H: *Les pauses respiratoires survenant au cours du sommeil chez l'homme* 1967 C R Soc Biol 161 634-9
15. Doll E, Kuhlo W, Steim H, & Keul J: *On the development of cor pulmonale in the Pickwick syndrome* 1968 Dtsch Med Wochenschr. 93(49):2361-5
16. Dement WC: *The study of human sleep: a historical perspective* Thorax1998 53 (Suppl 3) S2-7
17. Guilleminault C, Tilkian A, & Dement WC: *The sleep apnea syndromes* Annual Reviews 1976 465-484
18. Kryger M, Roth T, and Dement WC eds: *Principles and practice of sleep medicine*
19. Remmers JE, De Groot WJ, Sauerland EK, & Anch AM: *Pathogenesis of upper airway occlusion during sleep* 1978 J Appl Physiol 44 (6) 931-8
20. Phillipson EA: *Sleep apnea - A major health problem;* New England Journal of Medicine 1993, 328 (17), 1271
21. Pierson DJ Tracheostomy from A to Z: 2005 *Historical context and current challenges* Respiratory Care 50 (5) 473-5
22. Henke KG & Piper AJ: *Sleep pioneer remembers the early days* 2001 Advance for Managers of Respiratory Care 10 (10) 10
23. Sullivan CE: *Disorders of breathing in sleep,* Modern Medicine of Australia March 1980, p7-17
24. Kuhlo W, Doll E, Franck M: *Exfolgreiche behandlung eines Pickwick syndromedurch eine dauertrichael canule* 1969 Med Wochenschr 94 1286-90
25. Lugaresi E, Coccagna G, Mantovani M, Brignani F *Effects de la trachéotomie dans les hypersomnies avec respiration periodique* Rev Neurol 1970: 123 267-268
26. Fujita S, Conway W, Zorich F, Roth T: *surgical correction of anatomicabnormalities in obstructive sleep apnea syndrome*:uvulopalatopharyngoplasty (UPPP) Otolaryngol Head Neck Surgery 1981, 89: 923-934
27. Han d, Wang J, Ye J, Yang Q, Li Q, Song C, Chen X, Lin Y : *Value of preservation of uvula in uvulopal atopharyngoplasty* Zhonqha Er Bi Yan Hou Ke Za Zhi 2000 35 (3) 215-218 (in Chinese)
28. Sundaram S, Bridgman SA, Lim J, Lasserson TJ *Surgery for obstructive sleep apnoea* Cochrane Database of Systematic Reviews 2005 Issue 4
29. Lim J, Lasserson TJ, Fleetham J, Wright J Lim J, Lasserson TJ, Fleetham J, Wright J. *Oral appliances for obstructive sleep apnoea*. Cochrane Database of Systematic Reviews 2006
30. Smith I, Lasserson TJ, Wright J: *Drug therapy for obstructive sleep apnoea in adults:* Cochrane Database of Systematic Reviews: Reviews 2006
31. Barsh L: *The Origin of Pharyngeal Obstruction during Sleep*; Sleep Breath. 1999;3(1):17-22
32. Davidson TM *The Great leap Forward: The anatomic basis for the acquisition of speech and obstructive sleep apnea* Sleep Medicine 2003 4 (#) 185-94
33. Davidson TM, Sedgh J, tran D, Stepnowsky CJ Jr Sleep Medicine 2005 6 (6) 497-505
34. Sullivan CE, Berthon-Jones M, Issa FG, & Eves L: *Reversal of obstructive sleep apnoea by continuous*

ResMed Corp. - Ex. 1030
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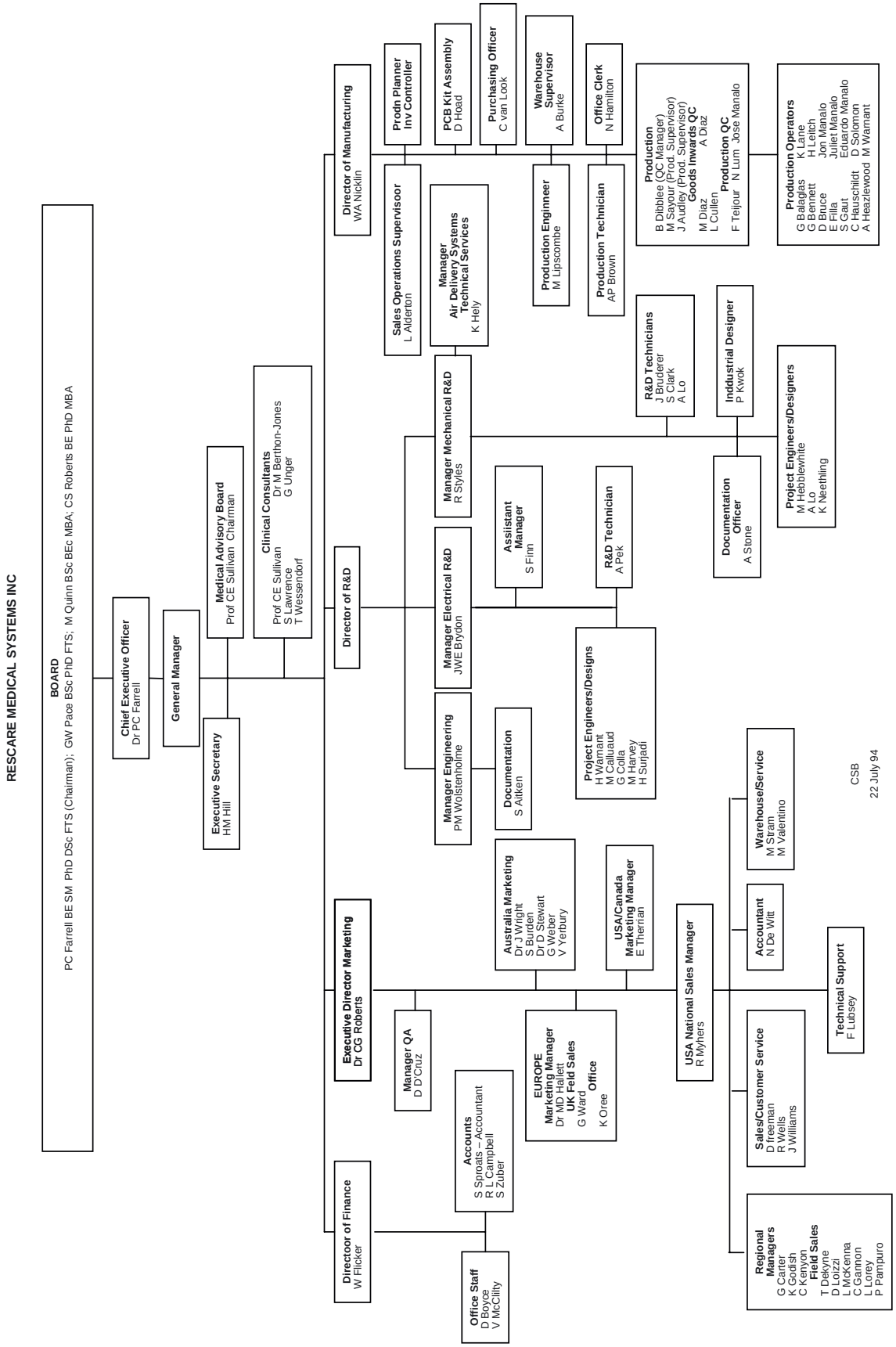
positive airway pressure applied through the nares Lancet 1981, 862-5

35. Wagner DR, Pollak CP, & Weitzman ED:*Nocturnal nasal-airway pressure for sleep apnea* 1983 New Eng J Med, 308, 461-2
36. Rapoport D, Sorkin B, Garay SM, & Goldring RM: *Reversal of the "Pickwickian Syndrome" by long-term use of nocturnal nasal-airway pressure;* New Eng J Med 1982,307 (15) 931-3
37. Block AJ, Faulkner JA, Hughes RL, Remmers JE, & Thach B: *Clinical conference in pulmonary disease. Factors influencing upper airway closure;* Chest 1984, 86 (1) 114-22
38. Pearce S & Saunders P: *Obstructive sleep apnea can directly cause death* 2003 Thorax; 58 (4) 369
39. Lax E: *The mould in Dr Florey's Coat* 2005 Abacus 206-208
40. AASM Task Force:*Sleep-related breathing disorders in adults: Recommendations for syndrome definition and measurement techniques in clinical research*, 1999 Sleep 22 (5) 667-689
41. Shapiro CM, Catterall JR, Oswald I, Flenley DC: *Where are the British sleep apnoea patients* 1981, Lancet 5 Sep, 523
42. Lavie P *Incidence of sleep apnea in a presumably healthy working population. A significant relationship with excessive daytime sleepiness* 1983 Sleep 6, 312-8
43. Jennum P, Sjol A *Epidemiology of snoring and obstructive sleep apnea in a Danish population, age 30-60:* J Sleep research 1992, 1: 240-244. The subject is reviewed in Young 2002 below.
44. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S: *The occurrence of sleep-disordered breathing in middle-aged adults:* 1993 New England Journal of Medicine 328 (17) 1230-1235
45. Young T, Peppard PE, Gottlieb DJ: *Epidemiology of obstructive sleep apnea* 2002 American Journal of Critical Care Medicine 165, 1217-1239
46. Hiestand DM, Britz P, Goldman M, Phillips B: 2006 Chest; 130: 780-786
47. Leger D *The cost of sleep-related accidents: a report for the National Commission on SleepDisorders Research Sleep* 1994; 17:84-93
48. Millman RP, Kimmel PL, Shore ET, Wasserstein AG 1985 *Sleep apnea in hemodialysispatients: the lackof testosterone effect on its pathogenesis* Nephron 40 (4) 407-10
49. Hallett M, Burden S, Stewart D, Mahony J, Farrell PC 1995 *Sleep apnea in end-stage renal disease patients on hemodialysis and continuous ambulatory peritoneal dialysis* ASAIO J 41 (3) M435-41
50. Hallett MD, Burden S, Stewart D, Mahony J Farrell PC 1996 16 Suppl 1: S429-33
51. Chan CT 2006 *Sleep apnea with intermitten themodialysis Time for a wakeup Call,* J Am Soc Nephrol 17 3279-3280
52. Finkelstein Y, Meshorer A, Talmi YP, Zohar Y *The riddle of the uvula* 1992 Otolaryngol Head Neck Surg 107, 444
53. Cotton RT *Uvulopalatopharyngoplasty*1993 Arch Otolaryngol 109 502
54. Bartlett CA, McLean AN, Wozney M, 2004 Entrepreneurship goes global, Harvard Business Review 26 April 2004
55. Berthon-Jones M *Feasibility of a self-setting CPAP machine Sleep* 1993, 16 S120-123
56. Condos R, Norman RG, Krishnasamy I, Peduzzi N, Goldring RM Rapoport DM 1994, *Flow limitation as a noninvasive assessment of residual upper-airway resistance during continuous positive airway pressure therapy of obstructive sleep apnea* Am J Respir Crit Care Med 150 (2) 475-80
57. Redline S, Pack AI 2006 *Rising to meet an unmet public health need: sleep medicine and the pulmonary community* American Review of Respiratory and critical care medicine 174 487-488
58. Elshaug AG, Moss JR, Southcott AM, Hiller JE *Redefining success in airway surgery for obstructive sleep apnea: A meta Analysis and synthesis of the evidence* Sleep 30 (4) 2007 461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THE LANCET, APRIL 18, 1981

REVERSAL OF OBSTRUCTIVE SLEEP APNOEA BY CONTINUOUS POSITIVE AIRWAY PRESSURE APPLIED THROUGH THE NARES

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Summary Five patients with severe obstructive sleep apnoea were treated with continuous positive airway pressure (CPAP) applied via a comfortable nose mask through the nares. Low levels of pressure (range 4·5–10 cm H_2O) completely prevented upper airway occlusion during sleep in each patient and allowed an entire night of uninterrupted sleep. Continuous positive airway pressure applied in this manner provides a pneumatic splint for the nasopharyngeal airway and is a safe, simple treatment for the obstructive sleep apnoea syndrome.

Introduction

THE syndrome of obstructive sleep apnoea is a common disorder, particularly in middle-aged overweight males.[1-3] The underlying problem is sleep-induced occlusion of the oropharyngeal airway, which results in multiple apnoeic episodes during sleep. There is severe fragmentation of sleep and, as the disease progresses over months or years, greater degrees of asphyxia occur; the duration of apnoea frequently exceeds two minutes and the arterial haemoglobin oxygen saturation falls below 50%. Remarkably, the patient may be unaware of his nightly struggle for breath. Rather, his major symptoms are those of excessive daytime sleepiness and snoring. The nocturnal asphyxia eventually causes a variety of clinical presentations including cardiac arrhythmias, pulmonary hypertension and right heart failure, systemic hypertension, severe morning headache, intellectual and personality changes, and polycythaemia. The true cause of these findings may not be suspected. The disease is a recognised cause of sudden "unexpected" death.[2,3]

In the obese subject, weight loss may reduce the number of obstructive episodes. Other measures such as neck collars[4] and respiratory stimulants (progesterone[5,6] or protryptyline[7]) are less satisfactory. The only effective treatment now available is a tracheostomy which is left open at night.[8,9] This immediately results in disappearance of the excessive daytime sleepiness, and the life-threatening complications of hypoxaemia, such as arrhythmias and cor pulmonale, improve dramatically within days. In patients who do not have any of the immediately life-threatening complications, a decision to do a tracheostomy is invariably difficult, despite the knowledge that the disease is progressive. We describe here a method which has prevented upper airway occlusion for an entire night of sleep in each of five patients with severe obstructive sleep apnoea.

Methods

Theoretical Background

Existing evidence supports the hypothesis that the sleep-related upper airway occlusion is passive. Remmers et al.[10] have suggested that the subatmospheric pressure in the airway during inspiration sucks the tongue and soft palate against the posterior oropharyngeal wall. Guilleminault et al.[11] have found evidence that there is a failure of the dilator action of pharyngeal muscles during obstructive apnoea. The pre-existing conditions which would allow suction-collapse of the oropharyngeal airway are a combination of increased upper airway resistance (e.g., congenitally small airway, nasal polyps, tonsillar or adenoid enlargement) and a normal or excessive[11] sleep-induced reduction of muscle tone in the palate, tongue, and pharynx (fig. 1). To provide adequate airflow the subject with a pre-existing high upper airway resistance must generate more subatmospheric airway pressure than a normal subject, and therefore more suction pressure in the oropharyngeal airway during inspiration. The forces favouring airway collapse are the suction pressure generated within the airway during inspiration, and gravity (particularly the weight of the tongue and jaw). The forces resisting collapse are the tissue elastic components and muscle tone. Loss of muscle tone in sleep causes a further narrowing of the oropharyngeal airway and increased resistance; thus greater suction pressures are required to sustain airflow. At some critical point the tongue and soft palate are sucked onto the posterior oropharyngeal wall, causing complete occlusion (fig. 1). The aim of the present study was to test the hypothesis that continuous positive airway pressure applied through the nares would act as a pneumatic splint and prevent upper airway occlusion by pushing the soft palate and tongue forward and away from the posterior oropharyngeal wall.

Fig. 2 is a schematic diagram of the method. Two soft plastic tubes were shaped to fit snugly in each naris. The other ends of these tubes were inserted into a lightweight wide-bore tube. This arrangement was strapped to the patient's face. A medical grade silicone rubber ('Silastic No. 382', Dow Corning, Midland, Michigan, U.S.A.) was then run over the nose and nares to provide a comfortable seal. Continuous positive pressure was produced by connecting one end of the wide-bore tube to a vacuum-cleaner blower motor with variable speed control. The other end of the wide-bore tube was led

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Fig. 1—Mechanism of upper airway occlusion and its prevention by CPAP.

When the patient is awake (upper panel) muscle tone prevents collapse of the airway during inspiration; during sleep the tongue and soft palate are sucked against the posterior oropharyngeal wall (middle panel). CPAP with low pressure provides a pneumatic splint and keeps the airway open (lower panel).

away from the patient and was narrowed with mechanical resistance. The resistance of the circuit was chosen so that a high bias flow (20–40 l/min) was sustained for the range of pressures required at the nose. Pressure was measured continuously via a catheter inserted into one nasal tube (Statham 'PM 131 TC') and airway CO_2 was sampled continuously via a catheter in the other nasal tube and measured with a CO_2 meter (Godart 'Capnograph'). The blower motor was installed in a box lined with acoustic material, which reduced the noise level to that of a fan.

All-night Sleep Studies

Three all-night sleep studies were done in each patient. In the first study the diagnosis of severe obstructive sleep apnoea was established. Sleeping posture (supine, prone, lateral, and sitting) had no effect on the occlusive episodes. The second study, done 6 weeks to 7 months later, was a night of control observations immediately before a third all-night study during which CPAP was applied. The second two studies were done with the patient sleeping in the supine position. Sleep state was assessed with two electroencephalographic (EEG) records (C_3/A_2,C_4/A_1 positions), a postural (submental or nuchal) electromyographic record, and two ocular movement records. Electrocardiogram and heart rate were recorded continuously. Arterial haemoglobin oxygen saturation was measured with a Hewlett Packard ear oximeter and chest wall and abdominal movements were recorded with a circumferential inductance device ('Respitrace', Ambulatory Monitoring Inc., Ardsley, N.Y., U.S.A.). In the control study, airflow at the nose and

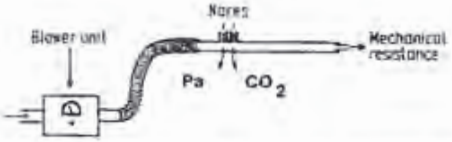

Fig. 2—Diagram of apparatus used to provide continuous positive airway pressure through the nares.

Pa = airway pressure; CO_2 = FCO_2.

mouth was monitored by a pressure transducer inserted into a loose-fitting, lightweight plastic face mask which covered both nose and mouth. Face masks were not used in the original diagnostic studies. All variables were recorded with a Grass model 78 16-channel EEG polygraph system. Sleep was staged according to standard criteria.[12]

Clinical Summaries

All five patients had a long history of noisy snoring and in the past 1–5 years had complained of excessive daytime sleepiness. The sleepiness had seriously interfered with the patient's life. For example, patient 1 had been forced to stop work in the building industry because he would fall asleep while working on scaffolding and while driving. Patient 3, a company executive, often fell asleep during important office meetings; and patient 4 had lost his job as a clerk because he fell asleep at his desk every afternoon. Patient 5, a boy of 13, had been considered mentally retarded. However, a large component of this retardation was secondary to his inability to stay awake at school. All five patients were normal on physical examination. Four, however, seemed to have a narrow oropharynx. Radiography of the upper airway did not identify any underlying abnormality. Respiratory function and arterial blood gases were normal. Three of the five patients refused tracheostomy.

Results

The control study confirmed the presence of severe obstructive sleep apnoea in all five patients—cyclic episodes of apnoea, interrupted by four or five loud snoring breaths, for the entire night of sleep. The mean apnoea index[3] in non-rapid-eye-movement (NREM) sleep was 62 apnoea episodes per sleep hour (range 33–97), the mean apnoea duration was 35 s (n = 434, range 16–70 s), and the mean of the lowest levels of haemoglobin oxygen saturation during apnoea was 84% (range 71–95%).

As described previously,[13] the duration of apnoea was longer in REM sleep (mean 45 s, n = 265, range 22–122 s) and the levels of haemoglobin oxygen saturation were lower (mean 73%, range 48–92%). The mean apnoea index in REM sleep was 64 apnoea episodes per sleep hour (range 48–85). Comparison with the original diagnostic studies showed no lessening in the severity of disease. Specifically, there were no statistical differences in the apnoea indices, duration of apnoea, and levels of oxygen saturation.

Continuous positive airway pressure completely prevented the upper airway occlusion in each of the five patients. The upper airway occlusion could be turned off and on simply by increasing or reducing the level of positive airway pressure. A typical record is shown in fig. 3. The first part of the tracing shows the characteristic cyclic occlusive apnoea with progressive asphyxia followed by a transient arousal with a few gasping breaths. The application of 4·5 cm H_2O of continuous positive airway pressure through the nares completely abolished the occlusion (arrow A). Within two minutes of unobstructed breathing this patient went into

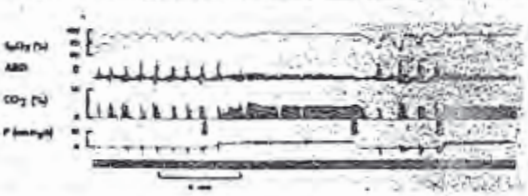

Fig. 3—Part of pen record from patient 2.

SaO_2(%) = arterial haemoglobin oxygen saturation; ABD = abdominal movement, upward deflection indicating diaphragm descent; CO_2(%) = airway carbon dioxide sampled from one nostril; P = pressure recorded from the second nostril. The hatched bar is NREM sleep; the closed bar is REM sleep. For explanation of arrows, see text.

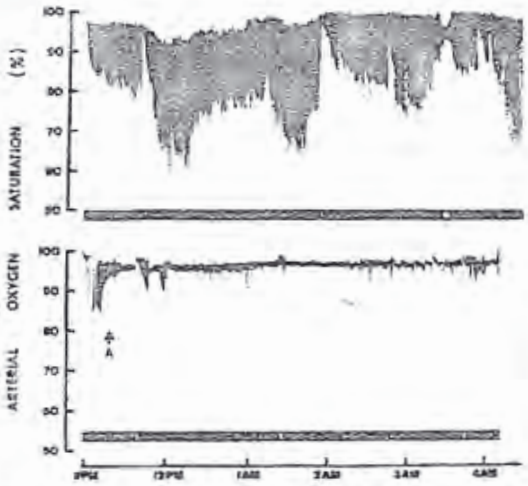

Fig. 4—All-night slow recordings of arterial haemoglobin oxygen saturation from patient 4.

Control night (upper panel); test night (lower panel); hatched bar, NREM sleep; closed bar, REM sleep; open bar, awake. CPAP of 7·0 cm H_2O was applied at arrow A and sustained for the rest of the night. See text for details.

REM sleep. Note the episodes of central apnoea typical of this sleep-state. Reduction of the nasal pressure (arrow B) caused the immediate return of occlusion. The longer apnoeic periods and greater falls in haemoglobin oxygen saturation are typical of REM sleep. Increasing the nasal pressure (arrow C) again completely abolished the occlusive episodes.

The all-night slow recordings of arterial haemoglobin oxygen saturation from the control night (upper panel) and test night (lower panel) of patient 4 are shown in fig. 4. The repetitive decreases of saturation shown here for the control night were typical of the control night in each of the five patients. In the early part of the test night (lower panel, fig. 4) the patient showed the typical occlusive episodes. Continuous positive airway pressure of 7 cm H_2O was applied at arrow A and sustained for the rest of the night. This level of pressure completely abolished the occlusive episodes.

The small decreases of arterial haemoglobin oxygen saturation which occurred during the rest of the night resulted from short episodes of central apnoea in stage I NREM sleep and in REM sleep; these are normal findings for those sleep stages.

Once identified, the level of continuous positive airway pressure required to prevent upper airway occlusion required no further adjustment for the entire night. These pressures were 10·0, 4·5, 6·0, 7·0, and 4·5 cm H_2O in patients 1–5, respectively. No patient had difficulty sleeping with the nose-mask in operation. The short sleep-onset latency which is typical of this disorder was found on both control and test nights, and there was a pronounced increase in the time spent in stage III and IV NREM sleep and REM sleep on the test night (table). Two of the patients had very long episodes of REM sleep (90 min patient 1, 70 min patient 5) within seconds after the upper airway had been made patent with continuous positive pressure, and there was a reduction in the latency to REM sleep in all patients.

The immediate clinical response to one night of unobstructed sleep was remarkable. Each patient awoke spontaneously, was alert, and remained awake unprompted for the rest of the day. None of the patients had excessive daytime sleepiness for that day. One of the patients (patient 1) had been unable to stay awake for longer than a few minutes each day and for the three days before the test he was observed to be asleep with an occluded upper airway during most of the daylight hours. After the test night he remained awake for the entire day and was able to watch television for several hours—something he had been unable to do for years.

To evaluate whether the patients could continue to sleep with the nose-mask and continuous positive airway pressure after losing the pathological sleepiness which characterises this disease, further studies were undertaken. On separate occasions, two of the patients were treated with continuous positive airway pressure on three consecutive nights, after a control all-night study in which the nose-mask was in place but with positive pressure below the critical level for reversal of occlusion. In these patients the pattern of obstruction on the control night was identical with that seen previously. On the three treatment nights there were no episodes of obstructive apnoea during sleep while continuous positive airway pressure was maintained. Despite the absence of clinical and self-reported pathological sleepiness by the

SLEEP PROFILE ON CONTROL AND TEST NIGHTS

Patient	Age (yr)	Weight % predicted	Time of study	Sleep latency (min)		Total sleep time (min)	% NREM sleep		% REM sleep
				NREM sleep	REM sleep		Stage I, II	Stage III, IV	
1	40	109	C 23·29–06·02 T 22·20–05·57	0 0	127 0	381 417	65 38	0 21	35 41
2	52	92	C 22·14–05·43 T 23·58–05·35	4 0	147 51	385 288	81 54	0 14	19 32
3	55	108	C 22·38–05·25 T 22·52–05·28	3 5	80 51	376 372	77 51	3 20	20 29
4	48	186	C 22·42–05·56 T 23·30–04·40	0 2	96 90	416 310	72 26	2 45	26 29
5	43	80	C 23·23–05·39 T 22·39–05·28	2 0	256 0	362 364	72 40	18 26	10 34
Mean ± SE				1·8±0·8 1·4±1·0	141·2±30·9 38·4±17·2	384·4±9·2 350·2±23·0	73±3 42±5	5±3 25±5	22±4 33±2

C = Control night; T = test night.

second day after treatment, both patients were still able to sleep with the nose-mask and continuous positive pressure on the third night of treatment, and awoke spontaneously after total sleep durations of 446 and 330 min.

Discussion

Our simple method of reversing sleep-induced upper airway occlusion was remarkably effective in these five patients with severe disease. The fact that the occlusion could be turned off and on in each patient by increasing and decreasing the level of continuous airway pressure is proof that the therapy works. It cannot be argued that the method worked by keeping the patient awake or even at a light stage of sleep. On the contrary, each patient had a night of uninterrupted sleep—probably the first for months or even years— and there was a shift from the lighter stages of NREM sleep to stages III and IV NREM sleep. The abnormally short REM sleep latency and long REM sleep episodes found in some of the patients is typical of the rebound effect after sleep fragmentation or deprivation. The fact that each patient remained without any obstruction during these REM episodes is further evidence of the efficacy of the method, for it is in REM sleep that muscle tone is lowest and patients with obstructive sleep apnoea tend to be worst. Some patients have occlusive episodes only during REM sleep.

Tracheostomy is the most direct form of treatment and rapidly reverses the symptoms and life-threatening complications of obstructive sleep apnoea.[8,9] However, most patients are reluctant to have such therapy and many refuse. The decision to do a tracheostomy is usually difficult. Unless there are life-threatening complications such as arrhythmias or pulmonary hypertension and right heart failure, there are no absolute criteria for its use, despite the knowledge that the relentless, repetitive nocturnal asphyxia is probably causing tissue damage. Non-invasive forms of therapy are attractive to patient and clinician but to date none has been very successful. We believe our method will provide a useful adjunct to the treatment of this disorder.

A crucial question is whether patients will be able to tolerate the nose-mask after they recover from their pathological sleepiness. The fact that the two patients who were treated over three consecutive nights were still able to sleep without discomfort on the third night, despite loss of the pathological sleepiness, is encouraging evidence that this form of treatment can play an important part in the management of these patients. However, whether long-term treatment will be practical or whether treatment with continuous positive airway pressure over a short period will in itself reduce the frequency and severity of the obstructive episodes remains unanswered.

Irrespective of its potential for long-term treatment, the method is well suited to the in-hospital management of those patients with the difficult combination of lung disease and sleep-induced upper airways obstruction, and of those in whom obesity makes tracheostomy difficult or dangerous. Such patients frequently present with cor pulmonale as a direct consequence of severe nocturnal hypoxaemia. The use of nasal continuous positive airway pressure could play a major role in the initial management by rapidly reversing the hypoxaemia and pulmonary hypertension and providing time for other measures such as weight reduction to become effective.

Theoretical disadvantages of continuous positive airway pressure have been widely discussed.[14,16] Initially, inspiration is facilitated and expiration is impeded; the end-expiratory lung volume shifts to a higher level and a new balance between inspiratory muscle effort and lung elastic recoil is established. In animals a reflex activation of expiratory muscle occurs. The major concern with continuous positive airway pressure is that it reduces cardiac output and renal function. However, this is only a problem with pressures in excess of 10 cm H_2O. Less serious potential effects relate to pressure on the upper airway. Airway pressures of 5–10 cm H_2O would be expected to reduce mucosal blood flow. This could be an advantage, through reduction of mucosal oedema and swelling. Increased pressure in the sinuses might decrease drainage and cause problems in patients with pre-existing abnormalities. Drying of the airway mucosa, another possible complication, could be overcome by inclusion of a humidifier in the circuit. None of our patients had a sore or dry nose after the procedure.

Mechanical failure of the positive airway pressure device is another potential hazard. Occlusion of the exhaust line could theoretically cause hyperinflation of the lungs and perhaps even lung rupture. This can not happen if a low pressure pump, e.g., a fan, is used (maximum pressure say, 15 cm H_2O). Furthermore, because the pressure is applied only through the nares, the mouth should act as a blow-off valve. A more likely mechanical failure is that of a loss of pressure. If this did occur, it would simply return the patient to his usual state of upper airway obstruction. However, since the mouth is unoccluded by the apparatus he will be able to breathe room air at the moment of arousal and return of muscle tone. This is, in effect, a fail-safe system which would not be available if the method required a face-mask covering both the mouth and the nose. The inherent simplicity and safety suggest that home use will be possible.

This work was supported by grants from the Ramaciotti and Asthma Foundations and from the University Research Grants Committee. D. Lauff prepared the figures and J. Bevan typed the script.

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REFERENCES

1. Guilleminault C, Dement WC. 235 cases of excessive daytime sleepiness. *J Neurol Sci* 1977; 31: 13–27.
2. Lugaresi E, Coccagna G, Mantovani M. Hypersomnia with periodic apnoea. In: Weitzman E, ed. Advances in sleep research, vol. 4. New York: Spectrum Press, 1978.
3. Guilleminault C, van den Hoed J, Mitler M. Clinical overview of the sleep apnoea syndrome. In: Guilleminault C, Dement WC, eds. Sleep apnoea syndromes. New York: Alan R. Liss Inc, 1978: 1–12.
4. Hensley M, Read DJC. Intermittent obstruction of the upper airway during sleep causing profound hypoxaemia. A neglected mechanism exacerbating chronic respiratory failure. *Aust NZ J Med* 1976; 6: 481–86.
5. Orr WC, Imes NK, Martin RJ. Progesterone therapy in obese patients with sleep apnea. *Arch Intern Med* 1979; 139: 109–11.
6. Strohl KP, Brown R, Hensley MJ, Hallett M, Saunders NA, Ingram RH. Progesterone therapy for obstructive sleep apnoea. *Am Rev Resp Dis* 1979; 114: 171.
7. Clark RW, Schmidt HS, Schusi SF, Boudoulas H, Schuller DE. Sleep apnoea treatment with protriptyline. *Neurology* 1980; 28: 1287–92.
8. Coccagna G, Mantovani M, Brignani F, Parchi C, Lugaresi E. Tracheostomy in hypersomnia with periodic breathing. *Bull Physiopath Resp* 1972; 8: 1217–27.
9. Motta J, Guilleminault C, Schroeter JS, Dement WC. Tracheostomy and haemodynamic changes in sleep-induced apnea. *Ann Intern Med* 1978; 88: 454–58.
10. Remmers JE, de Groot WJ, Sauerland EK, Anch AM. Pathogenesis of upper airway occlusion during sleep. *J Appl Physiol* 1978; 44: 931–38.
11. Guilleminault C, Hill MW, Simmons FB, Dement WC. Obstructive sleep apnoea: electromyographic and fibroptic studies. *Exp Neurol* 1978; 62: 48–67.
12. Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. *(Natl Inst Health Pub 204)* Washington, DC: U.S. Govt. Printing Office, 1968.
13. Coccagna G, di Donato G, Versichi F, Grignoni F, Mantovani M, Lugaresi E. Hypersomnia with periodic apnea in acquired macroglossia. *Arch Neurol* 1976; 33: 769–76.
14. Venus B, Jacobs HK, Lias L. Treatment of the adult respiratory distress syndrome with continuous positive airway pressure. *Chest* 1979; 76: 257–61.
15. Kumar A, Falke KJ, Geffin B, Aldredge MB, Laver E, Lowenstein E, Pontoppidan H. Continuous positive-pressure ventilation in acute respiratory failure. *N Engl J Med* 1970; 283: 1450–56.
16. Bishop B, Hirsch J, Thursby M. Volume, flow and timing of each breath during positive-pressure breathing in man. *J Appl Physiol: Respirat Environ Exercise Physiol* 1978; 45: 495–501.

Endnotes

i Apnea is a word coined from the Greek to mean "without breath". Obstructive apneas arise from a blockage in the upper airway that prevents air entering the lungs even though muscles of respiration in the chest and diaphragm are working. Central apnea, mentioned later in the text is quite different. Here the airway is fully open, but the muscles of respiration are not functioning. The two forms frequently occur together to give mixed apneas. A third form of apnea is when breathing is withheld deliberately, as in deep diving.

ii OSA in antiquity is presented in greater depth in references 1 and 2, which were the source of this section. Later developments are covered in reference 3 and in textbooks.

iii Recent publications continue to support the view that it is too facile to suggest that obesity necessarily results from an inbalance between calorie intake and energy requirements. See for example *Frayling et al Science. 2007 May 11: 316 (58260:889-94).*

iv William Osler was born in what is now Ontario, in 1849. As a teenager, he began to follow his father's profession as an Anglican minister. Abandoning this for medicine, he studied at a Toronto medical school, then McGill university for his medical degrees. Following postgraduate training in Europe, he returned to McGill as a professor in 1874. Medicine at this time was in transition to a more scientific basis, and was expanding as a university subject. He went on to Chairs at University of Pennsylvania, then appointments at Johns Hopkins Hospital as first Chief of Staff, and Johns Hopkins University as one of the first Professors of Medicine. In 1905 he was appointed to the Regius Chair of Medicine at Oxford, where he stayed till his death in 1919 from the influenza pandemic.
While at McGill, Osler is credited with forming the first "Journal Club" to have group discussion of published work. Amongst his many accomplishments, Osler is credited with establishing the medical residency program in which students added to their formal instruction with clinical experience in hospitals.
Wikipedia has an extensive biography.

v A connection with OSA exists, as the US company Cephalon is currently promoting the drug Provigil (Modafinil) for sleepiness remaining from inadequate CPAP treatment. The drug has been prescribed in France since 1994 as a palliative treatment for narcolepsy. Modafinil is a racemate. Cephalon are now offering one isomer as Armodafinil.

vi William C Dement began his medical training at the University of Washington, where he obtained his BS in1951. His MD and PhD were obtained at the University of Chicago in 1957 and 1959. At Chicago, his research was with Nathaniel Kleitman. It was Kleitman who, in 1953, with Eugene Aserinsky made the first description of rapid eye movement (REM) sleep. Using an electroencephalograph, Kleitman and Dement determined the all night sleep patterns, and studied REM sleep in infants and in animals. Patterns of eye activity during REM sleep were related to the visual experience of the dream. In 1963 Dement joined the Psychiatry Department of Stanford University, where he remains a Professor of Psychiatry.
The following year Dement initiated a special narcolepsy clinic through which he demonstrated a relationship between narcolepsy and disordered REM sleep. Extending narcolepsy studies to animals, Dement discovered narcolepsy in dogs. Basic studies described neurochemical abnormalities of this disorder. Currently, research is focussing on the suprachiasmatic nucleus that oversees many of the body's rhythmic processes.
Importantly for sleep disordered breathing, in 1970, Dement established the world's first Sleep Disorders Clinic, bringing all-night polysomnography to bear on the study of sleep-related complaints. The Stanford Clinic effectively brought the study of sleep disordered breathing to the USA and the world outside Europe. A focus then was to relate quality of night-time sleep to daily function. With Mary Carskadon (later a Professor of Psychiatry at Brown University) in 1975, he developed the Multiple Sleep Latency Test as a measure of daytime sleepiness. The test remains the main determinant of excessive daytime sleepiness. The first few papers published on obstructive sleep apnea laid a firm foundation for subsequent more detailed studies.
Dement was co-founder of the Sleep Research Society in 1961. He was founding President of the American Sleep Disorders Association in 1975, and remained President for 12 years. He was heavily involved with the preparation of *Wake up America: A National Sleep Alert* that in 1992 drew attention to the cost of sleep disorders to the United States. Bill Dement was associated with ResMed in its early years, and remains a good friend. Wikipedia has a biographical entry.

vii This is believed to be the first clinic dedicated to sleep disorders. There is no published history of the introduction of clinics and teaching of sleep medicine as part of medical degree courses. Common belief is that both have had slow beginnings.

viii Despite his preoccupation with dogs, Phillipson was well aware of the clinical importance of sleep-disordered breathing in people. In 1993, when the seriousness of sleep disordered breathing was not widely recognised, he was author of an invited editorial (20) with the title *Sleep Apnea- a major public health problem* in the *New England Journal of Medicine*. In it, he likened the community cost of sleep apnea to that of smoking.

ix The terms tracheotomy (G tomē mouth) and tracheostomy (G stoma, mouth) are used interchangeably in the medical literature, for the cutting of a hole in the trachea (G tracheia artēria, rough artery), the air tube in the neck communicating between the larynx and the bronchi. Medical dictionaries are inconsistent. The procedure was referred to in Hindu and Egyptian texts from 3000+ years ago and in Roman and Arabian texts from the 3rd and 4th centuries AD. Since the organ involved is soft tissue, there is no material confirmatory evidence that the procedure was used in antiquity. The first account written by the surgeon who performed the operation dates from 1546 in Italy. An historical account of tracheotomy use is given by DJ Pearson (21).

x The hospital was founded in 1882 to commemorate the safe recovery of Queen Victoria's second son, Prince Alfred, Duke of Edinburgh, Earl of Ulster and Kent, following an assassination attempt during a Royal visit to Sydney. This was the first Royal tour of Australia. The grateful Prince honoured the hospital by authorising his Coat of Arms to be used as the new Hospital's crest. Alfred's older brother, King Edward VII, granted the "Royal" prefix in 1902. The would-be assassin was an Irishman, Henry James O'Farrell. He was tried and hanged within 6 weeks, despite a plea for clemency from the Prince. The defence plea was of insanity, though O'Farrell had known sympathies with the Irish independence movement. The event fired considerable and lasting sectarian and nationalist feelings in the Colony.

xi John Read, in whose memory the Asthma research Fellowship was established, had a brilliant career in thoracic and general medicine at Sydney University. When aged 39 he became the

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youngest ever Professor in Australian Academia. He suffered an untimely death when aged 42.

xii The Cecile Lehman Mayer Award is given by the American College of Chest Physicians for the best research papers on chest medicine/surgery. Applicants must be physicians of residency or fellowship status and under age 35.

xiii In 1983, editorial comment (5) on a paper reporting results of oropharyngeal surgery for treatment of snoring and obstructive sleep apnea made no mention of CPAP as a treatment. This authoritative comment on OSA, said that "In our present state of knowledge, tracheotomy is the only certain cure for life-threatening obstructive sleep apnea in adults".

xiv This historic paper laid the foundations of a new research area of medicine. ResMed was built on it, as was a global industry. Sullivan has given a more detailed description of his early experiments in an *American Thoracic Society conference (2006, Symposia abstracts, Sleep and Biological Rhythms 4 (s1), A1-A6. doi: 10.1111/j.1479-8425.2006.00241.x Abstract)*. In this he notes that the first patient treated in February 1981, was a 40-year-old man with severe sleep apnea who had refused tracheotomy. In 2006, the man remained healthy and was still using CPAP. This gives him the world record for length of CPAP use.

xv The vortex blower is a special type of fan that provides high volume, low pressure output. The impeller or fan, has a large number of radial blades with wider flat ends rotating at relatively high speed (3,600 RPM) in a channel around the periphery. Inlet and outlets are located on this channel. As the blades pass the inlet, air is drawn into the space between adjacent blades, where a vortex is created, with centrifugal force throwing the air through the outlet. Thus it can act as a blower or a vacuum pump. A description is given at http://www.carymfg.com/Rcs.htm.
Professor Sullivan's familiarity with the vortex system has appeared in two directions. In addition to ventilation with applied nasal positive pressure, he had experimented with negative pressure ventilation through a cuirass around the trunk. Suction was applied from a vortex blower identical with that used in his CPAP applications.

xvi Gerald E McGinnis, Founder of Respironics in 1976, claims to have introduced SleepEasy as the world's first commercial CPAP in 1985 (http://www.respironics.com/Facts.asp). Sullivan's device had been sold through Medical Gasses Australia many years prior to that. Medical Gasses later became distributor of ResMed's products. Respironics was listed on NASDAQ as RESP in 1988.

xvii The main treatment for kidney failure was hemodialysis. For this treatment the circulatory system of patients is connected two or three times per week through tubes to a complex machine that pumps their blood over a semipermeable membrane. Low molecular weight waste products, such as urea and creatinine, pass through the membrane to be flushed from the system. A Dutch physician, Willem Kolff, had improvised the first effective device in occupied Holland in 1944. His device was made from drink bottles, a washing machine, and a drum using blood in tubes made of cellophane food packaging film. Dialysis took 6 hours. A version of the Kolff device that had been improved at the Peter Bent Brigham Hospital, was used through the Korean War (1950-1953). In 1956, an innovative young company, Baxter Healthcare, made the first commercial dialysis machines. In 1964, Dow Chemical introduced hollow fibre capillary membranes through which blood could be passed. While effective, the procedure is demanding on the patient, and requires blood anticoagulants that have a degree of toxicity.
Peritoneal dialysis had been an unrealised dream since 1923. In that year, George Ganter, in Germany, introduced into the peritoneum, a sterile solution of electrolytes, made hypertonic with glucose. He demonstrated removal of toxins and excess water, but had numerous practical problems of drainage and infection. Boen's system of 1960 was very cumbersome, with a requirement of 40 litres of sterile fluid to be instilled through a catheter that was then removed, leaving a hole to be covered in the abdomen. Tenckhoff's catheter could be permanently inserted with tissue ingrowth into Dacron cuffs to protect from infection. The design incorporated holes made to a size that allowed gravity drainage without blocking. In 1978, Baxter began supplying peritoneal dialysis fluid in 2 litre plastic bags. These could be aseptically attached to the catheter, fluid drained into the peritoneal cavity, and after an hour or two drained out under gravity. It was no accident that Baxter knew how to handle sterile biological materials in flexible plastic bags. Since 1959 they had been supplying intravenous solutions. In 1970, their IV bag facility was the largest in the world. By 1978, Robert Popovich and colleagues, biomedical engineers at the University of Texas, had worked out how to administer 5 exchanges of 2 litres per day for continuous ambulatory peritoneal dialysis (CAPD). In 1979, Baxter released the first complete kit, consisting of three glucose concentrations for controlling ultrafiltration, a solution transfer set, and a "prep" kit to help control infection at the bag-catheter connection. CAPD then became a going concern.
A peritoneal dialysis kit looks pathetically simple. Yet after feasibility was first demonstrated, it took over 45 years of continuous research by some of the smartest and most dedicated people, in the richest and most technologically advanced country in the world, before there was a commercially viable product.

xviii The University of New South Wales is one of the largest research-focussed universities in Australia, and it is a member of the international Universitas21 (http://www.universitas21.com/). Its origins go back to the Sydney Mechanics Institute, founded in 1843. This became the Sydney Technical College in 1878, and by act of Parliament in 1949, the New South Wales University of Technology. The name was changed to University of New South Wales in 1958. In 2006 there were 9 Faculties with 6,500 staff teaching 200 undergraduate and 500 postgraduate courses. Undergraduate numbers were 40,000, of which more than 9,000 were from overseas. The medical faculty introduced in 1961, had 4 teaching hospitals in 2006.

xix In the early 1970s, Farrell published a dozen or so papers in collaboration with leading experts, including Scribner and Popovich. They were looking at practical aspects of membrane performance and dialyser reuse, as well as interactions between urine and blood components with each other and the membranes of hemodialysis. In Sydney, Farrell's university group collaborated with hospital renal specialists on topics such as dialysis regeneration, membrane characteristics and performance, patient interaction with the dialyser, anticoagulation techniques, and effects of molecular size of blood components on performance of dialysis. By 1980, emphasis had shifted to CAPD. This was still a new technique needing fine-tuning. Collaborations included projects with microbiologists on the critical subject of peritonitis; others were on theoretical aspects of transport through the peritoneal membrane, decline of renal function, sleep apnea as a comorbidity with end stage renal disease, and effect of CAPD on nutritional and metabolic stability.

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xx In 1990, Peter Farrell coopted nine like-minded prominent citizens to form a Strategic Imperatives Committee. Its purpose was to examine why "For decades Australia has had a sleepy, inflexible, overly protected, non-competitive economy", with the objective to devise "how Australia could achieve economic integrity and maintain it for the long term". The Committee's Report with the title "Wealth Creation in Australia" issued in December 1991. The Report made 14 recommendations covering designation of a national icon, through microeconomic reform, to dole payments.

xxi BCMR was formed in 1986, as an autonomous outpost of the giant Baxter Healthcare organisation. The Centre's introductory publicity brochure shows "the BCMR Team (who were) committed to the success of Australian medical research through its commercial application". They are grouped rather self consciously looking at papers on a table. Peter Farrell, as Vice President, R&D, Baxter World Trade, was its Director; General Manager Chris Lynch was a chemical engineer and economist with experience as a management consultant in Amsterdam and Sydney; Research Manager Phil Hone, a chemical engineer with experience in Baxter's Sydney R&D, and in membrane technology with Memtec; and Charles Barnes a consultant with experience as a research manager in technology and science based industries.

Baxter Healthcare, although founded in 1931 on intravenous solutions, had grown by acquisitions and applied research, into a broad-based medical manufacturer and service provider, and hospital supply company. It had diagnostic and respiratory divisions, made recombinant products, vaccines, and blood fractions. In Australia, Baxter had expertise in sterile manufacture of solutions in plastic bags for peritoneal dialysis, intravenous injection and blood collection, and parenteral and enteral nutrition. They were also involved with all aspects of hemodialysis.

While no pressure was exerted to relate support for projects to those close to Baxter' s interests, it was logical to give a proportion of support to areas where BCMR had expertise. Thus there was support for projects on end-stage renal disease, nutrition in diabetes, membrane performance, and continuous ambulatory dialysis. Other projects of interest were on DNA probe technology, noninvasive diagnosis of IgA nephropathy, pre-ESRD nutrition, and microalbinuria diagnostic. Examples of proposals that were declined include a single use syringe, skin stapler, vaginal speculum, lipids in parenteral nutrition, polymeric antimicrobials, and immunomodulation.

BCMR links with the University of New South Wales were strong. As the Foundation Director of the University's Centre for Biomedical Engineering, Peter Farrell retained the title of Honorary Director of the University's post-graduate Centre for Biomedical Engineering, and was a Visiting Professor of the University with responsibility for supervision of postgraduate students. It was Peter Farrell's connections to the University, his strong support for academic research, his passion for research of value to the community, and his talent for lateral thinking that led to a project that benefited the University, but not in the manner intended.

One of Farrell's ideas was for Baxter to build, at no cost to the University, a six story building with two floors for the University's Postgraduate Centre for Biomedical Engineering (CBME), two floors for BCMR, and two floors at the University's pleasure. The cause for consternation was that the building would be sited on the main campus of the University. Not just on campus, but adjacent to, and connected by a bridge to the University's biosciences building. The response to this unique charitable act was dramatic. Students distributed pamphlets likening their proposed benefactor to Godzilla. Staff organised protest meetings and petitions against the encroaching tentacles of the multinational. Against this, Baxter sent a senior executive to emphasise at public meetings that Baxter had no intention to interfere in University affairs or their educational or research programs. This turmoil continued for many months during which the building was designed with cooperation of BCMR and CBME staff, contracts were let, and footings laid, at a cost to Baxter of 1 million 1990 dollars. Eventually Baxter decided to withdraw. The building was completed, CBME got new research quarters, and BCMR retreated to the suburbs. At the opening ceremony in 1992, not a word was mentioned of the $1 million graciously donated by the big multinational, nor the time and energy Peter Farrell and his colleagues had provided to make the building a suitable location for university research. The building was named for a senior University administrator. Essentially the only qualification acknowledged at the opening ceremony was the number of handshakes he had made in his administrative career.

And there were more dramas to come.

xxii Prior to 1986, Nobel prizes in medicine or related topics had been awarded to Howard Florey (penicillin, 1945), Macfarlane Burnett (immunology, 1960), John Eccles (neurology, 1963), and John Cornforth (enzyme chemistry and biosynthesis 1975). Lawrence and William Bragg had won the physics award in 1915 for inventions in x-ray crystallography. X-rays as a technology and knowledge of crystal structures of complex organic molecules are basic to progress in medical science. Since BCMR was formed, Nobel prizes have been won in purely medical topics by Peter Doherty (immunology, 1996), and Barry Marshal and Robin Warren (bacteriology and gastroenterology, 2005).

These people made tremendous advances to knowledge that must have contributed to community health. Their contribution to community wealth is not easy to document, but was not apparent in Australia. In 1986 the entire income of the research institutions, as far as I could determine was made up from grants, donations, and bequests.

This is not to suggest that winning a prize is a necessary recognition of outstanding work. Sir Gustav Nossal, himself a Nobel nominator, is well qualified to recognise excellence in science. He has noted at least two contributions that are worthy of awards: http://www.abc.net.au/rn/scienceshow/stories/2001/386419.htm. One of these, Professor Donald Metcalfe's colony stimulating factors, has been manufactured in quantities sufficient to treat cancer patients numbering in the millions. The reward and any flow-on from further research has most likely gone to Amgen, its US manufacturer.

xxiii Such approaches were not always welcomed. There was then a breed of academic for whom industry was anathema. These days the phenomenon is hard to understand, as experience has shown that an academic becoming a multimillionaire is not necessarily an inhibitor to his academic research. A pertinent example is illustrated by Eric Lax in his biography (37) of Howard Florey and the commercial development of penicillin. The same attitudes were struck many times in BCMR. The most striking was a short interview in Perth with the person in charge of the University of WA research liaison office. The circumstance arose through a company affiliated in some way with Baxter that had money, in the order of $100,000, that it was obliged to spend in return for being granted a contract. The company did not know nor care where the money went. When this largesse was explained to the officer, his words were that it came from a multinational that only wanted to steal the results of the university's work, and he was not going to give them access to anything. He was replaced soon after.

There were other cases where leaders of projects or institutions

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showed a well developed colonial cringe by not granting interviews on the stated assumption that their projects were too sophisticated to be understood by an Australian company.

There is also no doubt that these attitudes are changing, and that both State and Federal governments are deliberately promoting collaborations between academic and institutional scientists with the people who can derive community benefits from their work. Maybe the high profile success of ResMed has contributed to a change of attitude. It might also be noted that the Company has contributed many millions of dollars to applicants through Company sponsored and personal charitable Foundations.

xxiv This term is a translation of the French tour d'ivoire, which the critic Saint-Beuve used to describe the attitude of poet Alfred de Vigny in 1837. It is used most often in reference to intellectuals and artists who remain complacently aloof.

xxv Christopher Lynch BE (Chem Eng, Sydney) BA (Economics, Macquarie) came as the first employee of Baxter Centre for Medical Research from an international construction company, Austin, where he was Managing Director of the Australian subsidiary. He had international experience as Manager of the Amsterdam office for three years.
Coincidentally Austin was the contractors for construction of a new facility years after Lynch's departure.

xxvi Jim Bruderer was an instrument maker trained in Switzerland. His contribution to the development of CPAP was remarkable.

xxvii However we are informed in 2007 by Australian sales staff that some of these flow generators are still being used, with the owners resisting offers of more modern alternatives.

xxviii Fans come in a number of forms. The usual desktop or ceiling form for moving air in a room, are known as axial fans, since air moves in a direction parallel to the axis of spin across the area swept by the fan blades. They are capable of moving large volumes of air at low pressures. The advent of DC brushless motors made this type of fan suitable for cooling electronic equipment. Centrifugal or radial fans have an impeller with blades operating within a housing so that air is drawn in near the axis and is thrown centrifugally at right angles to the axis to an outlet in the casing. Greater pressures may be obtained from a given volume of air. They are used as leafblowers, for example. A third type known as a cross flow or tangential fan, is a version of the centrifugal fan with an impeller shaped like a squirrel cage, having vanes at the periphery of the rotor, parallel to the axis of rotation. Wikipedia has an informative entry under "Fan (implement)".

xxix The company was later absorbed into ResCare.

xxx Michel Calluaud came from a cognac making family in Cognac. Escaping from occupied France before completing an engineering degree, he joined the Free French Air Force in North Africa, completing engineering studies in the Department of Civil Aviation. Migrating to Australia in 1950, he worked on early versions of Distance Measuring Equipment and Instrument Landing Systems. Subsequently, with IBM, he collaborated in the design and installation of the first computer-controlled aluminium smelter in Australia, at Bell Bay, Tasmania. Later he joined medical device firms, Ausonic and Telectronics. He eventually became Research Manager at ResCare before retiring through ill health. After completing the IBM project he worked at the Powerhouse Museum, formerly known as the Museum of Applied Arts and Sciences. There, he had a workshop equipped for making electronic displays for the Museum. He was able to use these facilities after completing the Museum project. ResMed has since sponsored projects at the Museum.

xxxi From July 1984 to July 1988, Mr Flicker served as Executive Director of the Medical Engineering Research Association, an Australian biomedical industry association. From July 1988 to June 1989, Mr Flicker served as Business Development Manager at Baxter Center for Medical Research Pty Ltd, a subsidiary of Baxter International, Inc. Mr Flicker holds a B.E. with Honors in mechanical engineering and a Master's in Biomedical Engineering from the University of New South Wales.

xxxii Sherrill Burden had experience in renal nursing in Australia and Canada prior to joining BCMR. She stayed only 3 months with ResCare before leaving. Later she returned to ResMed, eventually becoming Director of Clinical Education and Support.

xxxiii The association of endstage renal disease with apnea was noted in 1985 (48). This and other early papers were reporting prevalences as high as 73% in small numbers of patients with OSA. Peter Farrell and associates from ResCare (49) and ResMed (50) were drawing attention to apnea in patients on both hemo- and peritoneal dialysis in 1995 and 1996. By then the association between OSA and cardiovascular disease was well known. Surprisingly there were few nephrologists who paid serious attention. A reviewer in 2006 (51) could still indicate that it was time for a Wake-Up call.

xxxiv Mr Nicklin was appointed Vice President, Manufacturing of ResCare in January 1990. From October 1987 to November 1989, he served as the Manufacturing Director of Valuca Pty Ltd, a manufacturer of small electrical appliances. From November 1989 to January 1990, Mr Nicklin was a consultant to Hanimex, a manufacturer of photographic products. Mr Nicklin holds a certificate in mechanical engineering. He left the company in July 2005.

xxxv Technologists usually use "elastomer" as the generic term for materials with elastic, rubber-like properties Judges in the Australian appeal litigation consistently referred to the material as silicon.

xxxvi By Justice Gummow, later appointed to the High Court, the highest Court in the country.
It may be viewed at http://www.austlii.edu.au//cgi-bin/disp.pl/au/cases/cth/federal_ct/unrep5804.html?query=rescare
http://www.austlii.edu.au//cgi-bin/disp.pl/au/cases/cth/federal_ct/unrep6112.html?query=rescare

xxxvii Fisher & Paykel's financial year 2000 report records that their "HC100 humidifier was our first product in the CPAP market. During the year, we launched our second product - a combined humidifier and flow generator, the HC200". Interestingly, "As an aside, I feel that this unique product illustrates the synergy between our Healthcare and Whiteware businesses, as it uses the same Fisher & Paykel developed ECM motor as our unique DishDrawer® dishwasher." The HC 100 humidifier had been used with ResCare's flow generators.

xxxviii Michael Berthon-Jones completed his medical degrees at Sydney University. He spent 2 years working in respiratory medicine in a Sydney hospital before returning to Sydney University to work under Professor Sullivan toward a PhD on the control of breathing during sleep. He was one of the co-

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authors on Professor Sullivan's original description of nasal CPAP for treatment of obstructive sleep apnea. As a clinician he gained firsthand experience with the glue-on mask. He served some time as a clinical consultant to ResCare before joining staff in 1990. While with ResMed he made valuable contributions to clinical research and computer control of airflow devices, particularly AutoSet, VPAP, and AutoSet CS. All were state-of-the-art at the time. Michael eventually left the company in 2004 to pursue artistic interests.

xxxix At the time there was much research directed toward the same end. Berthon-Jones presented his results as an unrefereed conference paper in 1992. In the report of the proceedings, published in 1993 (55) Dr David Rapoport of New York University graciously acknowledged that Berthon-Jones' work was "a few month's ahead of the rest of us". Dr Rapoport, who had published the first confirmation of Sullivan's successful nasal CPAP treatment, went on to publish a complete description of flattening of the respiratory airflow versus time curve during flow limitation (56). His publication in a refereed journal is generally quoted as the origin of this feature.

xl Theresa B Young PhD has been one of the dominant figures in the epidemiology of sleep apnea and its consequences. She is an editor of journals Sleep, Sleep Medicine Reviews, and Sleep Research Online. She is on Program Committees of the American Academy of Sleep Medicine and the American Thoracic Society, is Divisional Head (epidemiology) of WHO worldwide project on sleep, and was on the Task Force for Sleep-Disordered Breathing Syndrome Definitions and Measurement Techniques in Clinical Research. In the 1980s Terry Young acquired experience and expertise with epidemiological studies in the Wisconsin area. These were on associations of drinking water chlorination with female mortality (n=8,029); lifestyle components with oral cancer (n=623), diet and risk factors for herpes and colorectal cancer (n=252 + 618 controls), alcohol consumption and breast cancer (n=1,082), and nitrate in drinking water and gastric cancer. In 1989 she initiated the Wisconsin Sleep Cohort Study as an open-ended study with thousands of participants, whose health was to be followed for decades. Such studies require ongoing financial support over the working life of generations of committed technologists and professionals, and collaboration with specialists in other areas. The resultant conclusions are compelling. On the sleep side, this study was the first to show that shorter sleep periods reduce blood levels of the appetite controlling hormone leptin, and increase levels of ghrelin, a hormone thought to stimulate food intake. Much subsequent data has been on obstructive sleep apnea. By 1993, data was provided to establish the high prevalence of the disorder in the community, and in women. Subsequent studies showed associations between OSA and hypertension, stroke, diabetes, motor vehicle accidents, and women in menopause. In collaboration with other large-scale studies, OSA was shown to be associated with psychiatric disorders (Veterans' Administration). With the Sleep Heart Health Study, having 60,000 participants, OSA was shown to be associated with excess weight, changes in weight, and an APOE gene.

xli The position with sleep-disordered breathing is complicated by its propensity to progress over many decades from insignificant beginnings through a pathological continuum of increasing severity, with no well-defined stages, toward fatal consequences. Symptoms are extremely variable between individuals. Simple, intermittent snoring may confer little detriment to quality of life. In the darkness it contributes to thickening of the carotid artery with atheromas threatening ischemic stroke. OSA initially may not cause excessive daytime sleepiness. Later, sleepiness could cause traffic accidents. Sufferers of congestive heart failure brought on by, or exacerbated by, OSA may feel no subjective tiredness, though objective tests show significant deficits in performance. Gaining valid information on disease severity requires time-consuming measurements with multiple measuring instruments. For statistical purposes agreed arbitrary points need to be taken as the reference points. Lack of standard definitions of abnormal events during sleep prevented comparison of studies from different sources. Such factors inhibited the gathering of reliable data on a scale large enough to give convincing results.

The American Academy of Sleep Medicine, in 1995, decided to set up a Task Force in conjunction with The European Respiratory Society and The Australasian Sleep Association to develop recommendations for syndrome definition and measuring techniques in clinical research for sleep-related breathing disorders. The report (38) in 1999 identified and defined obstructive sleep apnea hypopnea syndrome, respiratory effort-related arousal events, central sleep apnea-hypopnea syndrome, Cheyne-Stokes breathing syndrome, and sleep hypoventilation syndrome.

Quite early in the modern history of OSA, reports from the Stanford Clinic (17), and others, identified many of the serious sequelae. They could not identify the prevalence, as the samples were small and not representative of a community. Patients had been referred to medical specialists because of serious symptoms. First guesses were made by such clinicians based on their experience.

Such was the position when Colin Sullivan approached Peter Farrell in 1986. Sullivan's paper had drawn a quick response (39) from representatives of a sleep research laboratory and a respiratory unit studying breathing irregularities during sleep in Edinburgh. These people knew about OSA, and they had the polysomnography instruments to diagnose it. Over a period of three years, studies on 120 patients by polysomnography found only 3 patients with OSA as defined by Guilleminault. One of the authors had been conducting research into sleep for 20 years "and saw his only case of obstructive sleep apnea ten years ago". The inference was that things were different in the USA.

By 1986 there was only one other report of prevalence. Peretz Lavie (42) had investigated a sample of workers, by questionnaire. Those males reporting excessive daytime sleepiness, were given a confirmatory PSG sleep study. This showed a connection between sleepiness and OSA, without establishing community prevalence of OSA. This and other studies (43) not designed to give valid community prevalence data were indicative of a significant prevalence.

Sullivan's estimate in 1986 was a prevalence of about 2%. For someone whose experience was with end stage renal disease, this was a very high rate. Community prevalence of end stage renal disease is difficult to acquire. The condition varies enormously between subgroups with different promoting factors. Community prevalence is more likely to approximate 0.1%, rather than 1%. This level was sufficient support a major division in Baxter. A product marketable to 2% of the population would be an attractive commercial proposition to Farrell.

To acquire reliable prevalence data on a community is demanding on resources of time, finance, manpower, infrastructure, and skills of data acquisition and management. Altogether a rare combination. With a disease serious enough to have an effect on morbidity, large numbers of people may need to be studied for decades, or the working lifetimes of several PhD students. Fortunately, the subject attracted the attention of Terry Young, Professor of Population Health Sciences, in the School of Medicine and Public Health of the University of Wisconsin, Madison. A sample of 602 adults aged between 30 and 60 years working in State Government departments, were recruited from

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the Wisconsin Sleep Cohort. Polysomnography results showed an AHI ≥5 to be present in 24% of men and 9% of women (44). When excessive daytime sleepiness was considered, prevalence of coexisting AH≥5 was found in 4% of men and 2% of women. For AHI≥ 15, there was an estimated prevalence of 9% men and 4% women. These levels were rather higher than expected at the time, particularly for women. Male sex and obesity were strongly associated with sleep-disordered breathing.

Since 1993, there have been many reports of OSA prevalence, varying somewhat depending on definitions, selection methods, and protocols. Young and coworkers (45) critically reviewed available prevalence data in 2002. Most subsequent authors select Young's 1993 figures when applying data to a population. The review (45) goes beyond prevalence, to cover the state of OSA knowledge at the time. A poll of the National Sleep Foundation in 2005, which included the Berlin questionnaire, concluded that as many as one in four Americans could benefit from evaluation for OSA (44). In 2006 there has been enough data from sales to confirm surveys that showed the market is bigger than anything Sullivan and Farrell could have dreamed of in 1986.

xlii Making a quantitative determination of health costs is difficult at the best of times, depending on definitions. With sleep disorders, *Access Economics* made a major assessment in 2004 published as *Wake Up Australia,* in 2005. The 96 page report concluded that sleep disorders cost Australia $10.3 in 2004, with OSA making the major contribution.

xliii John Brydon BA (Hons, Natural Sciences and engineering, Cambridge), MSc (Medical Electronics and Physics, London), PhD (Biomedical Engineering, University of New South Wales, had worked in the UK National Health Service as a design engineer from 1972 to 1988, when he was Deputy Director of the Department of Medical Physics at Hammersmith Hospital and the Royal Postgraduate Medical School, London. From 1989 to 1991 he was Senior Signalling Engineer with Philips Communications Pty Ltd Melbourne, designing analog and digital signal Processing radio products. He continued designing, manufacturing and marketing digital signal processing equipment in a private capacity until joining ResCare in 1993. He left in 1997 to become an academic at Adelaide University and to consult in these and related fields. His publications include 15 US and Australian patents on biomedical engineering topics.

xliv US Patent 5,148,802 by Mark H Sanders and RJ Zdrojkowski issued on 22 Sep 1992, with a priority date of 22 Sep 1989 and was assigned to Respironics. Sanders' first publication in the medical literature was in *Chest 1990 98, (2) 317-324*. A German paper in *Anaesthetist 1989 38 (9) 452-8* describes a similar device, using the acronym BIPAP for a new form of augmented ventilation.

xlv Australian patent 560,360 had a difficult conception, a complicated birth, a troubled life, and an early death. Its short life provides many lessons for all associated with it. Some of these are explained at length by the inquisition:
http://www.austlii.edu.au//cgi-bin/disp.pl/au/cases/cth/federal_ct/unrep6846.html?query=rescare.

The initial mistake was that the inventor filed the Provisional Application that establishes the priority date of the invention, 6 days after the same data was open to public inspection in the journal *Lancet*. This alone would have invalidated the patent, except that at a cost of time and money, it was established that the journal had not been available in Australia at the date of filing. By this chance it was not an issue at the trial.

The next fundamental difficulty was for the patent attorney drafting the provisional specification. The invention in reality was a method of treatment of a patient. The apparatus was rather ordinary, though used in a novel manner. Patenting of methods of treatment of humans had never been allowed in Australia at the time. It was one of those unresolvable problems that keep disputing lawyers busy reiterating arguments over and over again to each other. In the end, it was the apparatus that had to be patented. The key novelty, as determined by the Court was a couple of tubes in person's nose. This had novelty, but with dubious practical utility, as the tubes were glued there. The complete specification, filed one year after the provisional specification, had advanced the technology to the point where a fibreglass cast individually made for each nose, was glued on to the nose with silicone adhesive. The tubes then became optional attachments, the subject of a claim, to a manifold made as part of the nose cover. That is the tubes, which were to become the bone of contention, remained firmly up the nose.

The trial judge took all these difficulties in his stride, validating the patent.

Three Court of Appeal Judges disagreed and revoked the patent. Their reasons give insight more into the operation of legal minds than patent law.

Whether methods of treatment should be patentable was clearly an issue of national importance and so worthy of serious and lengthy debate. Accordingly, each Judge gave vent to learned opinions. These had the significance and authority of a coin toss, since opinions differed and no verdict was issued.

The official reason for revoking was that the Complete Specification was not fairly based on the Provisional Specification. At first sight this seemed unreasonable, since the text of the Complete Specification embodied the Provisional Specification in its entirety, with suitable editorial changes to fit the new format, and correction of a typographical error. Of course reasons had to be given Claim by Claim to illuminate this serious decision. The problem here was that the apparatus of the provisional patent consisted mainly of two tubes entering the nostrils, and being glued in place to make the seal. The final specification had as its first claim the gluing of a cover to the nose. The tubes became an option in a later claim. To revoke the patent, the Judges had to show that these tubes did not appear in the final specification, though they were the subject of a claim and were shown in diagrams. The solution was simple. With the authority of three Judges of the Court of Appeal, the tubes were declared not to exist. Not only were there no tubes, but also the new apparatus was not, according to the Judges, sealed to the nose. The abstract, text, and claims spoke repeatedly of the seal. The words of three judges, are "…the device disclosed in the complete specification does not provide for a seal around the patients nose …" and "…there are no tubes entering the patient's nose…", and several more of a similar nature. In dismissing individual Claims, the Claim referring to tubes was not mentioned. It was revoked with no reason given. Other independent claims were revoked without reason.

The diagrams accompanying the text showed expertly drawn tubes side by side on the manifold, with numbers identifying them in the text as "tubes". Judges' unflattering authoritative comment on this artwork was "Even if the drawings could be read as providing an option of having nostril attachments or not (and I do not think they can be so read …)".

Since the claims of the complete specification were not fairly based on the original provisional specification, the complete specification would itself be novel and could claim priority of its date of filing. The Judges specifically excluded this option because of the prior art disclosed in the *Lancet* publication. This was the same apparatus and procedure on which the complete specification was not fairly based.

The ultimate authority on any legal matter in Australia is the

High Court. Leave must be sought to take this final appeal, as that Court is more concerned with matters of state than competence of the judiciary or trivia of technology. In this case the High Court representatives declined to hear an appeal.
http://www.austlii.edu.au//cgi-bin/disp.pl/au/other/hca/transcripts/1994/S75/1.html?query=rescare.
The High Court representative admitted that mistakes were made, saying that none were material. The reason for denial was that the original documents were not properly prepared. This had escaped comment by a trial judge and three appeal Judges.

xlvi Mr Abourizk joined the Company as General Counsel in July 1995. From June 1993 to June 1995 Mr Abourizk managed the Sydney office of Francis Abourizk Lightowlers, a legal partnership specializing in intellectual property matters. From March 1989 to May 1993 Mr Abourizk was Deputy Manager of Sirotech Legal Group, a technology transfer company. During the period from March 1986 to February 1989 Mr Abourizk became a Senior Associate in the Intellectual Property Group of an Australian national law firm Corrs Pavey Whiting & Byrne. Mr Abourizk received B.Sc. (Hons) and LL.B. degree from Monash University and Graduate Diploma in Intellectual Property from University of Melbourne. Mr Abourizk is admitted to practice before the High Court of Australia, the Supreme Court of Victoria (Barrister and Solicitor) and the Supreme Court of New South Wales (Solicitor).

xlvii The effect can be visualised by comparing the side profile of a gorilla, an "ape-man" such as Australopithecus, Neanderthal man, and modern man, the latter somewhat egotistically and possibly inaccurately named *Homo sapiens.* Interestingly H sapiens is the only animal to have an uvula, the association suggesting that this is the source of wisdom.

1986 BCMR Team

1992 Australian Export Award Finalist Peter Farrell with an Official

1991 First Award small Business Achievement
Chris Lynch, Peter Farrell

1992 AGM Standing: John Plummer
Seated: Shirley Sproats, Michael D'Ambrosio (accountant), Ken Hely, Michael Hallett Seated rear right: Helen Hill

1991 Australian Export Award Finalist Colin Sullivan, Peter Farrell with Officials, Lyon Park Road

1992 AGM Front: Colin Sullivan, Chris Lynch, Chris Roberts, Michael Quinn, Ross Harricks Standing: Wal Flicker

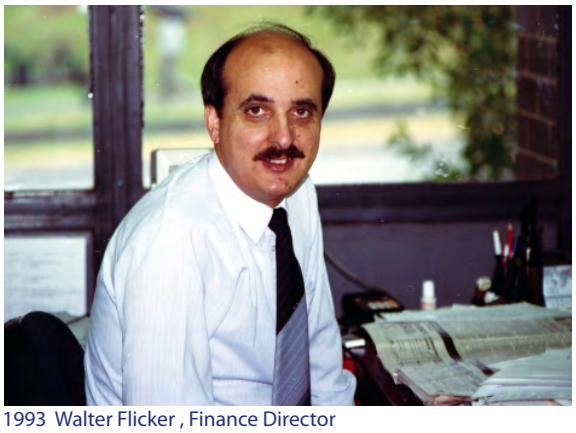
1992 Peter Farrell, Chairman & CEO

1992 Peter Farrell in Production area

1992 Christopher Lynch, General Manager

1992 Chris Lynch & Peter Farrell, Lyon Park Road

1992 Christopher Roberts, Executive Director



1993 Walter Flicker , Finance Director

1992 Staff Meeting L to R Clockwise- Brian Dibblee, David D'Cruz, George Weber, Peter Wolstenholme, Peter Farrell, Helen Hill, Albert Pek, Michael Calluaud, Judy Harris, Ken Hely, Bob Styles.

1992 Chris Lynch, Michael Calluad

1993 Ken Hely, Bob Styles

1992 Shirley Sproats, Accountant

1992 Michael Hallett, Marketing Manager Europe

1993 Deirdre Stewart, Australia Marketing

1993 Albert Pek, R&D Technician

1995 Bob Styles, Manager Mechanical R&D

1993 John Reedy with servers

1992 John Brydon, Manager Electronic R&D

1993 Chris Van Look, Purchasing

1992 Chris Roberts, Colin Sullivan

1993 Peter Wolstenholme, Manager Engineering

1992 Seated: Jim Bruderer, Amanda Piper
Standing: Radio Host Dr James Wright, Colin Sullivan

1993 Judy Harris

1993 David D'Cruz, Albert Pek

Standing: Bill Niklin, Balancing Fans

1993 Government Support

1993 Shane Finn

1993 Hubert Warnant, Project Engineer

1993 Marie Warnant

1993 Dani Dumic

Jos Manalo, Production Operator

Guy Bennett

Sherrell Burden

1995 Export Award

1995 Export Award Refreshments

1995 Export Award Audience 1

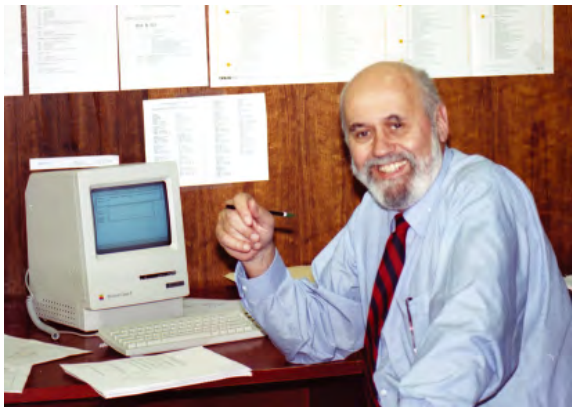
1994 Sylvia Aitken, Documentation.

1995 Export Award Audience 2

1994 Hary Surjadi

Robin Schmitt

Sylvia, Graeme, Sherrill, Cassandra, Dani


1995 Vic Yerbury, Australia Marketing

1995 Allan and Helen Hill, Peter Farrell

1995 Fay Everett, Clinical Research

1995 Chel Hauschildt and Friends

1995 Malcoolm Hebblewhite, Project Engineer

1995 Shirley Sproats, Hary Surjadi and Friends

1995 George Weber, Australia Marketing, Wal Flicker

1995 Sylvia Aitken, Alan and Helen Hill and Friends

Clinton Stewart 2007

Greg Colla, John Brydon,& Hary Surjadi supervising student

Helen Hill

John Byers, Barry Beattie

Marcelo Diaz 2007

Mark Abourizk 2007

Suzanne Zuber

Paul Farrell