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GUEST EDITORIAL

Sleep apnea—Past, present, future

This edition of *Sleep Medicine Reviews* summarizes various perspectives on the past, present and future of sleep apnea research. Einstein once stated that ''the distinction between past, present and future is only a stubbornly persistent illusion''. However that comment was delivered by Einstein to physicists rather than sleep medicine clinicians. Perhaps in contrast, the rapid growth in knowledge about sleep apnea is not an ''illusion'' but an obvious fact and the future increase in information about sleep-breathing disorders is likely to be astronomical.

The first publication by Peretz Lavie[1] appears from a glance at the title a historical review into the origins of sleep apnea syndrome. In many ways, historical reviews are different beasts from the experimental research more familiar to our day-to-day experience. The nature of ''evidence'' is different—Lavie's paper depends largely on his interpretation of mainly secondary historical sources. Historical research is often characterised by revisionism and re-revisionism as perceptions change and time unfolds. In Lavie's case the revisionism is refreshing—it has always been curious, given the great impetus to clinical neurophysiology with the development of electroencephalogram (EEG) recordings, that no-one had observed the sleep fragmentation of obstructive sleep apnea, a disorder that would have been common enough in research volunteers and neurological patients. Lavie highlights the almost stumbling discovery of the link between disturbed breathing, arousals and daytime sleepiness. He also indicates the over-attribution to Burwell's case report.[2] This was presumably due to a follower effect—busy researchers being far too preoccupied with the paper in hand and unwilling to check the original sources where instead there was a readily available convenient historical reference such as Burwell's paper cited by a previous author. Another important outcome of this historical review is to re-establish the importance of European contributors to the beginnings of sleep apnea research. Nevertheless with any historical review dependent on secondary sources, there may be a protracted period of disputed recollection following publication of Lavie's manuscript—we look forward to this!

Importantly, Lavie's paper really comes in two parts—a historical section that ends abruptly with the creation of the name ''sleep apnea syndrome'' by Guilleminault, Tilkian and Dement from Stanford in the mid-1970s.[3] Many of us in the field wish that this name had never been invented—perhaps the Stanford group should have gone to a Madison Avenue advertising agency to provide the disorder with an alternate ''brand''. The word ''syndrome'' always seems to convey a rarer, curiosity status to medical conditions. In turn, this makes it difficult to explain to administrators that sleep apnea is a common disorder worthwhile of healthcare expenditure.

In the second part of the paper, Lavie dwells in the rather inexact science of bibliometry including the ''Top 20'' hit parade of authors on sleep apnea. Although this list of 19 men and 1 woman exemplifies a top echelon of researchers, it is inaccurate. Other names, not listed in Table 1, run through the ISI Web of Science will also yield over 50 publications. Such lists are biased towards clinical researchers and there may be others performing cutting-edge basic work. In addition, a country-by-country analysis is done but does this really measure true impact? Is it adjusted for impact factor or citation index? We speculate that one published papal edict on sleep apnea in a medical journal would have given the Vatican City a notional publication rate of approximately 10 publications/10,000 population given the small population of the smallest country in the world. Impact factor may also be tricky—there are some papers in the sleep field that have graced the pages of Nature, Science or New England Journal of

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Medicine (NEJM) and subsequently been elegantly disproved by subsequent studies published in lower impact journals. Even citation index can be problematic—think about how many times Burwell's paper must have been cited.

Rather than focus on a top list of 20 researchers or countries, perhaps it would be more informative to focus on some of the major discoveries in the field that have had lasting effects on research and disease management. We are not sure how much you can really reflect on the history of sleep apnea by bibliometric analysis and wonder whether Lavie's excellent paper should have stopped in the 1970s waiting for the dust of more modern times to settle before further reflection on more ''Burwellian'' misattributions. We would argue that after the discovery of the ''syndrome'', the introduction of continuous positive airway pressure (CPAP) therapy gave an enormous impetus to the field of sleep.[4] However, this impact was delayed because of a major lag in acceptance of this concept as investigators focused on surgical approaches in the 1980s. In fact many of the major research directions that developed in the 1980s such as better understanding of airway physiology, respiratory control and treatment were strongly stimulated at an international symposium in California in 1977.[5] This symposium was funded by a foundation established by Ray Kroc, the founder of MacDonalds. One could say the Golden Arches indirectly led to the Golden Airway, the pipeline of science underpinning the huge commercial developments in sleep apnea diagnosis and therapy.

One important line of research that has gained momentum over the past two decades has been the links between sleep apnea and cardiovascular disease. The comprehensive review by Luthje and Andreas[6] highlights an array of mechanistic epidemiological, and treatment studies, which support an independent role for obstructive sleep apnea (OSA) in promoting coronary artery disease and its associated complications. However we should be ever mindful of the fact that medical research is well populated with short-term intervention studies that too often fail to show effects after more rigorous investigation in long-term, large-scale randomised clinical trials. Although the important study by Marin et al.[7] was a significant watershed in terms of increasing the awareness of OSA as a marker of cardiovascular disease risk, it is at best an observational cohort study. Like other observational studies, it may well be confounded by unmeasured factors such as visceral abdominal obesity that are increased in OSA and are themselves strong determinants of risk. In addition, the lack of prospective randomised designs may result in treatment bias where CPAP refusers are the same people who refuse to stop smoking or take blood pressure or lipid lowering medications. The lack of any rigorously designed trials has to date been blamed on the ethical challenges associated with protracted treatment denial. However the time has come to put these concerns aside. Indeed, there are now several ongoing or planned long-term randomised controlled trials to assess the effect of OSA treatment on the incidence of new cardiovascular events. Although such trials represent a bold leap into the unknown, they will undoubtedly result in the dispersion of any lingering uncertainties over the need to treat OSA and ultimately improve healthcare delivery to people with this important disease.

The main weakness of these long-term studies is the need to use a mechanical device, CPAP, with variable compliance as the treatment modality. This problem is underscored by the comprehensive review by Hedner et al.[8] of pharmacological approaches to sleep apnea. Their review highlights one historical fact—that the absence of a viable pharmacological therapy for sleep apnea is arguably the single greatest limitation in clinical practice in sleep medicine. For some years, OSA researchers have been united in the hope that the next major milestone in the field could be the discovery of a specific and practical pharmacological treatment of sleep apnea. Much of the work highlighted in this paper deals with drug ''repurposing'' research aimed at treating sleep apnea, i.e., the use of existing drugs developed for other conditions and re-testing their efficacy for a new ''purpose''. Unfortunately the past and present reality is that progress has been disappointing. The future, however, holds enormous promise as the secrets concerning the functional neurobiology of sleep apnea pathogenesis are slowly unravelled, as more appropriate and specific animal models are developed and as the genetic basis underpinning sleep apnea becomes properly scrutinized (see later). As suggested by the authors, we need to understand inter-individual differences in sleep apnea pathogenesis and how this may relate to the response of particular patients to specific pharmacological therapies. It may be that certain patient target groups are sensitive to certain drugs—these target groups need to be phenotyped or if possible, genotyped. The latter would allow elegant pharmacogenomic research.

In this vein, the review by Riha et al.[9] examines in detailed fashion the limited data on genetic factors associated with hypertension and metabolic disease and how these relate to sleep disordered breathing. The review demonstrates that these

data are limited, and occasionally contradictory. For example, two equally large studies each examining about 1000 individuals have variably shown that the angiotensin–converting enzyme (ACE) D allele polymorphism is associated with either an increase[10] or a decrease[11] in the risk of hypertension in adults with obstructive sleep apnea/hypopnea syndrome (OSAHS).

Why have these discrepancies occurred and how do we decide which relationships are true? Strategies adopted to investigate other polygenic disorders particularly cardiovascular disease are relevant.[12,13] These studies highlight that tens of thousands, not thousands, of participants are probably required for association studies[10] and replication and validation of findings in multiple cohorts are absolutely essential. Such rigorous approaches are yet to be applied to the investigation of hypertension and metabolic disease in populations with sleep disordered breathing. However, they require the initial identification of robust findings before they can reliably dissect epiphenomena from direct or indirect associations. For these reasons, we advocate collaboration amongst researchers throughout the world in order to feasibly perform genome wide scans to identify novel genes that cause OSA or modulate its expression. The development of European sleep apnea research consortia and preliminary developments elsewhere highlight the potential of this approach in our field. Nevertheless, the challenge faced by us all is to apply these approaches in a setting which is especially problematic because of the constellation of many seemingly diverse and separate pathogenic processes which all culminate in obesity, metabolic syndrome and obstructive sleep apnea.[14] Novel unifying and evidence-based hypotheses linking these processes may ultimately prove to be enlightening. Metabolomic approaches may be useful, although no evidence for this were presented.

If successful, designer drugs targeting relevant genes to prevent, treat or modulate the expression of OSA become plausible and provide a solution to the dilemma discussed by Hedner et al.[8] This approach includes identifying genes that modulate the response of individuals to OSA—for example, genes that could potentially protect apneic individuals from sleepiness, hypertension or cardiovascular morbidity. Potentially, drug targets capitalising on known polymorphisms in the ACE gene could become useful therapeutically, provided preliminary findings can be reliably replicated.

Knowing history is necessary, but not sufficient, to prevent the mistakes of the past. The application of genetic, proteinomic and metabolomic approaches to sleep disordered breathing and its consequences is in its infancy. This means that we can learn from progress made in other fields of research. Whether this occurs, or past mistakes are simply repeated remains to be seen. As Einstein said "I never think of the future—it comes soon enough".

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