Ralph Lydic, Ph.D., Recipient of the 2012 Excellence in Research Award

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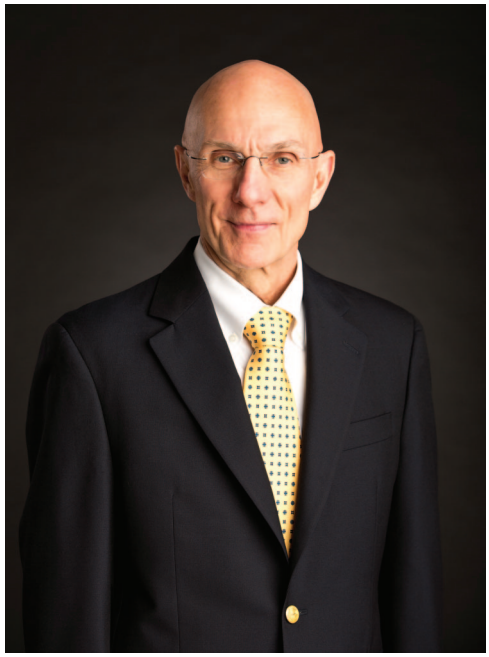
IN 1986, Lawrence J. Saidman, then Editor in Chief of ANESTHESIOLOGY, announced that the American Society of Anesthesiologists (ASA) Board of Directors had established an award for excellence in research.[1] In the ensuing quarter of a century, the Excellence in Research Award has come to be regarded as the highest honor our society can bestow on an investigator.[2] Ralph Lydic's research on the neurobiology of sleep and anesthesiology has helped lead our specialty to understand that anesthesiology can further enhance patient care by a systematic focus on issues previously considered the purview of neurology or sleep disorders medicine. Saidman's editorial noted that the ASA award recognizes research that (1) is mature and significantly advances anesthesiology and (2) fosters education and the scientific progress of our specialty.

If the forgoing criteria sound familiar, it is because in today's parlance these criteria also comprise the definition of research that is considered "translational."[3] Sleep-related research is the ultimate in cross-cutting, translational science. Restorative sleep is a health requirement for each of the 7 billion humans on earth. Normal sleep is diminished by trauma, surgery, pain medications, pain, and even by the environmental conditions of acute[4] and intensive[5] care units. Although sleep and anesthesia are distinctly different states, they share clinically relevant traits.[6,7] Lydic's research has focused on three areas where the linkage between sleep and anesthesia has the most translational relevance. These areas include arousal state-dependent respiratory depression, sleep and pain, and the neurochemical control of sleep and anesthesia. During most of his 13 yr at Michigan, Ralph has simultaneously directed three National Institutes of Health grants. His work has been funded continuously since 1988 by grants from the National Heart, Lung, and Blood Institute.

In 1999, I recruited Ralph to the University of Michigan as the Bert La Du Professor and Associate Chair for Research. Our interaction over the years gives me a detailed appreciation of the significant impact of Ralph's research on anesthesiology. Ralph has maintained a steadfast focus on efforts to understand the brain mechanisms by which states of sleep and anesthesia depress breathing. Shortly after the 1953 discovery of the rapid eye movement (REM) phase of sleep, data from anesthesiologists made clear that the ventilatory response to hypercapnia was depressed during states of anesthesia[8] and states of sleep.[9] Ralph's 1979 Ph.D. thesis from Texas Tech University identified brain regions that contribute to state-dependent (sleeping *versus* aroused) respiratory depression. His thesis research, in the laboratory of John Orem, demonstrated that regions of the brain known to regulate levels of behavioral arousal also significantly altered diaphragmatic and upper airway muscle function.[10,11] Ralph's research discovered that the discharge of laryngeal abductor muscles decreased progressively with the transition from wakefulness to sleep.[12] Ralph's thesis capped these pioneering studies by publishing the first electrophysiological evidence that the discharge of respiratory neurons in the pontine pneumotaxic center decreased during sleep.[13] These findings provided novel evidence for state-dependent depression of premotor, respiratory neurons that regulate phase-switching between inspiration and expiration. These initial studies set the stage for Ralph's future research that has identified brain regions and neurochemical systems contributing to the wakefulness stimulus for breathing. This wakefulness stimulus was a concept first postulated in the early 1960s by the 1987 recipient of the ASA Excellence in Research Award, B. Raymond Fink.[14] Ralph's early studies and his subsequent productivity were recognized in May 2012 when he received



Ralph Lydic, Ph.D., recipient of the American Society of Anesthesiologists 2012 Excellence in Research Award.

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the Distinguished Alumnus Award from the Graduate School of Biomedical Sciences of Texas Tech University.

During his postdoctoral training and junior faculty years at Harvard Medical School, Ralph won a National Research Service Award from the National Institutes of Health and scholarships to the neurobiology training programs of both the Cold Spring Harbor and Woods Hole Marine Biologic Laboratories. While at Harvard, Ralph continued his electrophysiological studies, working with postdoctoral mentors R.W. McCarley and J.A. Hobson in the Laboratory of Neurophysiology. Using microwire electrodes, Ralph obtained extracellular recordings from the same single neurons for several days at a time. These long-term recordings helped clarify the role of dorsal raphe neurons in the regulation of sleep and wakefulness. His work contributed to a model of sleep cycle control described in a paper that has become a citation classic.[15] The impact of Ralph's research during his Harvard years is clear from the inclusion of his research in contemporary textbooks devoted to sleep neurobiology[16] and sleep disorders medicine.[17]

In 1989, Julian Biebuyck recruited Ralph to serve as Division Chief of Anesthesiology Research at the Pennsylvania State University College of Medicine. Julian was also instrumental in recruiting Helen A. Baghdoyan from Harvard to Penn State. Ralph and Helen were married in 1987, and their union has resulted in one of the most productive couple collaborations in the history of anesthesiology research. Helen runs her own research program, and in 2004 she also brought honor to our department as recipient of a National Institutes of Health MERIT award. Ralph became a tenured Professor of Anesthesiology at Penn State in 1991, where he served as Chair of Anesthesiology Research while holding the Julian F. Biebuyck endowed chair in Anesthesiology.

In the mid- to late-1990s, Ralph published, in anesthesiology journals[18] and textbooks,[6] the shared circuits hypothesis, postulating that neural networks that evolved to generate sleep comprise the brain substrates that are most likely to generate and maintain states of anesthesia. This, to some extent, challenges what I was told when I entered anesthesia residency: "This is general anesthesia, it's not like they're sleeping." Subsequently his mastery of *in vivo* microdialysis combined with recordings of arousal states has enabled Ralph and his collaborators to demonstrate changes in brain acetylcholine levels before and after administration of opioids[19–21] and volatile anesthetics.[22,23] Further supporting the shared circuits hypothesis, Ralph and his colleagues have discovered that cholinergic neurotransmission in brain regions regulating sleep is also depressed by ketamine[24] and benzodiazepine receptor agonists.[25] Most recently, Ralph has extended the shared circuits hypothesis to show that in sleep-related brain regions, anesthetics also alter levels of γ-aminobutyric acid (GABA)[26,27] and the sleep-promoting molecule adenosine.[28,29] Conservation of function is supported when evidence repeatedly reveals that lower level phenotypes (genes, neurons, neurotransmitters) influence behaviors (sleep, sedation, anesthesia) that are similar in different species.[30] Many laboratories have published in this journal data that support the shared circuits hypothesis by demonstrating conservation of function in the regulation of wakefulness, sleep, and anesthesia.[31–40] Ralph's research has helped promote a new dimension in patient care by bridging the gap between clinical anesthesiology and sleep disorders medicine.[41]

This ASA award also recognizes that research provides the content for education, and it is important to briefly highlight examples of Ralph's career-long commitment to education. Laboratory mentoring is very much like training residents, and nearly 50 graduate students, medical students, and postgraduate fellows have benefited from Ralph's mentorship. The enthusiasm Ralph displays for his work has attracted more than 30 University of Michigan undergraduates, many of whom have earned coauthorship on abstracts and papers. Ralph and Helen founded and codirect the first comprehensive class on sleep offered at the University of Michigan. Nearly 1,000 undergraduates, graduate students, and sleep medicine fellows have now completed the 18-week class "Sleep: Neurobiology, Medicine, and Society." Finally, Ralph has earned this award through his service as a scientific citizen. He has reviewed as a full-time member of a National Institutes of Health study section while serving as president of the Sleep Research Society. He reviews grants for the U.S. National Science Foundation, the Israel National Science Foundation, and the U.S. Army Research Office. Ralph has contributed to the ASA by service on the Futures of Anesthesiology Committee and the Task Force on Fatigue for the Committee on Occupational Health. Ralph currently serves on the External Advisory Council for the National Space Biomedical Research Institute. Ralph is a founding member and serves on the board of directors of the Society for Anesthesia and Sleep Medicine. In addition to these many accomplishments, I especially value Ralph's loyalty, professionalism, and upbeat demeanor. I extend my congratulations for this ASA Excellence in Research Award to Ralph, and I look forward to having him as a colleague for many years to come.

References

1. Saidman LJ: ASA Award for excellence in research. ANESTHESIOLOGY 1986; 65:359
2. Miller RD: William L. Young, M.D., recipient of the 2009 excellence in research award. ANESTHESIOLOGY 2009; 111: 485–6
3. Hobin JA, Deschamps AM, Bockman R, Cohen S, Dechow P, Eng C, Galey W, Morris M, Prabhakar S, Raj U, Rubenstein P, Smith JA, Stover P, Sung N, Talman W, Galbraith R: Engaging basic scientists in translational research: Identifying opportunities, overcoming obstacles. Journal of Translational Medicine 2012; 10:72
4. BaHammam A: Sleep in acute care units. Sleep Breath 2006; 10:6–15
5. Hardin KA: Sleep in the ICU: Potential mechanisms and clinical implications. Chest 2009; 136:284–94
6. Lydic R, Baghdoyan HA: Cholinergic contributions to the control of consciousness, Anesthesia: Biologic Foundations. Edited by Yaksh TL, Lynch C, Zapol WM, Maze M, Biebuyck

JF, Saidman LJ. New York, Lippincott Raven, 1997, pp 433–450

7. Brown EN, Lydic R, Schiff ND: General anesthesia, sleep, and coma. N Engl J Med 2010; 363:2638–50
8. Eckenhoff JE, Helrich M, Hege MJ: A method for studying respiratory functions in awake or anesthetized patients. ANESTHESIOLOGY 1956; 17:66–72
9. Bellville JW, Howland WS, Seed JC, Houde RW: The effect of sleep on the respiratory response to carbon dioxide. ANESTHESIOLOGY 1959; 20:628–34
10. Orem J, Lydic R: Upper airway function during sleep and wakefulness: Experimental studies on normal and anesthetized cats. Sleep 1978; 1:49–68
11. Orem J, Lydic R, Norris P: Experimental control of the diaphragm and laryngeal abductor muscles by brain stem arousal systems. Resp Physiol 1979; 38:203–21
12. Orem J, Norris P, Lydic R: Laryngeal abductor activity during sleep. Chest 1978; 73:300–1
13. Lydic R, Orem J: Respiratory neurons of the pneumotaxic center during sleep and wakefulness. Neurosci Lett 1979; 15:187–92
14. Epstein RM: ASA Award: B. Raymond Fink. ANESTHESIOLOGY 1987; 67:456–8
15. Hobson JA, Lydic R, Baghdoyan HA: Evolving concepts of sleep cycle generation: From brain centers to neuronal populations. Behavioral and Brain Sciences 1986; 9:371–400
16. Steriade M, McCarley RW: Brain Control of Wakefulness and Sleep, 2nd edition. New York, Plenum Press, 2005
17. Kryger MH, Roth T, Dement WC: Principles and Practice of Sleep Medicine, 5th edition. New York, Elsevier, 2011, pp 1–1723
18. Lydic R, Biebuyck JF: Sleep neurobiology: Relevance for mechanistic studies of anaesthesia. Br J Anaesth 1994; 72: 506–8
19. Keifer JC, Baghdoyan HA, Lydic R: Sleep disruption and increased apneas after pontine microinjection of morphine. ANESTHESIOLOGY 1992; 77:973–82
20. Mortazavi S, Thompson J, Baghdoyan HA, Lydic R: Fentanyl and morphine, but not remifentanil, inhibit acetylcholine release in pontine regions modulating arousal. ANESTHESIOLOGY 1999; 90:1070–7
21. Osman NI, Baghdoyan HA, Lydic R: Morphine inhibits acetylcholine release in rat prefrontal cortex when delivered systemically or by microdialysis to basal forebrain. ANESTHESIOLOGY 2005; 103:779–87
22. Keifer JC, Baghdoyan HA, Becker L, Lydic R: Halothane decreases pontine acetylcholine release and increases EEG spindles. NeuroReport 1994; 5:577–80
23. Keifer JC, Baghdoyan HA, Lydic R: Pontine cholinergic mechanisms modulate the cortical electroencephalographic spindles of halothane anesthesia. ANESTHESIOLOGY 1996; 84: 945–54
24. Lydic R, Baghdoyan HA: Ketamine and MK-801 decrease acetylcholine release in the pontine reticular formation, slow breathing, and disrupt sleep. Sleep 2002; 25:617–22
25. Hambrecht-Wiedbusch VS, Gauthier EA, Baghdoyan HA, Lydic R: Benzodiazepine receptor agonists cause drug-specific and state-specific alterations in EEG power and acetylcholine release in rat pontine reticular formation. Sleep 2010: 33: 909–18
26. Vanini G, Wathen BL, Lydic R, Baghdoyan HA: Endogenous GABA levels in the pontine reticular formation are greater during wakefulness than during rapid eye movement sleep. J Neurosci 2011; 31:2649–56
27. Vanini G, Watson CJ, Lydic R, Baghdoyan HA: Gamma-aminobutyric acid-mediated neurotransmission in the pontine reticular formation modulates hypnosis, immobility, and breathing during isoflurane anesthesia. ANESTHESIOLOGY 2008; 109:978–88
28. Nelson AM, Battersby AS, Baghdoyan HA, Lydic R: Opioid-induced decreases in rat brain adenosine levels are reversed by inhibiting adenosine deaminase. ANESTHESIOLOGY 2009; 111:1327–33
29. Gauthier EA, Guzick SE, Brummett CM, Baghdoyan HA, Lydic R: Buprenorphine disrupts sleep and decreases adenosine concentrations in sleep-regulating brain regions of Sprague Dawley rat. ANESTHESIOLOGY 2011; 115:743–53
30. Reaume CJ, Sokolowski MB: Conservation of gene function in behaviour. Philos Trans R Soc Lond B Biol Sci 2011; 336:2100–10
31. Alkire MT, McReynolds JR, Hahn EL, Trivedi AN: Thalamic microinjection of nicotine reverses sevoflurane-induced loss of righting reflex in the rat. ANESTHESIOLOGY 2007; 107: 264–72
32. Chemali JJ, Van Dort CJ, Brown EN, Solt K: Active emergence from propofol general anesthesia is induced by methylphenidate. ANESTHESIOLOGY 2012; 116:998–1005
33. Luo T, Leung LS: Basal forebrain histaminergic transmission modulates electroencephalographic activity and emergence from isoflurane anesthesia. ANESTHESIOLOGY 2009; 111:725–33
34. Nelson LE, Lu J, Guo T, Saper CB, Franks NP, Maze M: The alpha2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. ANESTHESIOLOGY 2003; 98:428–36
35. Pal D, Lipinski WJ, Walker AJ, Turner AM, Mashour GA: State-specific effects of sevoflurane anesthesia on sleep homeostasis: Selective recovery of slow wave but not rapid eye movement sleep. ANESTHESIOLOGY 2011; 114:302–10
36. Pick J, Chen Y, Moore JT, Sun Y, Wyner AJ, Friedman EB, Kelz MB: Rapid eye movement sleep debt accrues in mice exposed to volatile anesthetics. ANESTHESIOLOGY 2011; 115: 702–12
37. Pillay S, Vizuete JA, McCallum JB, Hudetz AG: Norepinephrine infusion into nucleus basalis elicits microarousal in desflurane-anesthetized rats. ANESTHESIOLOGY 2011; 115: 733–42
38. Solt K, Cotten JF, Cimenser A, Wong KF, Chemali JJ, Brown EN: Methylphenidate actively induces emergence from general anesthesia. ANESTHESIOLOGY 2011; 115:791–803
39. Tung A, Herrera S, Szafran MJ, Kasza K, Mendelson WB: Effect of sleep deprivation on righting reflex in the rat is partially reversed by administration of adenosine A1 and A2 receptor antagonists. ANESTHESIOLOGY 2005; 102:1158–64
40. Weber B, Schaper C, Bushey D, Rohlfs M, Steinfath M, Tononi G, Cirelli C, Scholz J, Bein B: Increased volatile anesthetic requirement in short-sleeping Drosophila mutants. ANESTHESIOLOGY 2009; 110:313–6
41. Chung F, Hillman D, Lydic R: Sleep medicine and anesthesia: A new horizon for anesthesiologists. ANESTHESIOLOGY 2011; 114:1261–2