

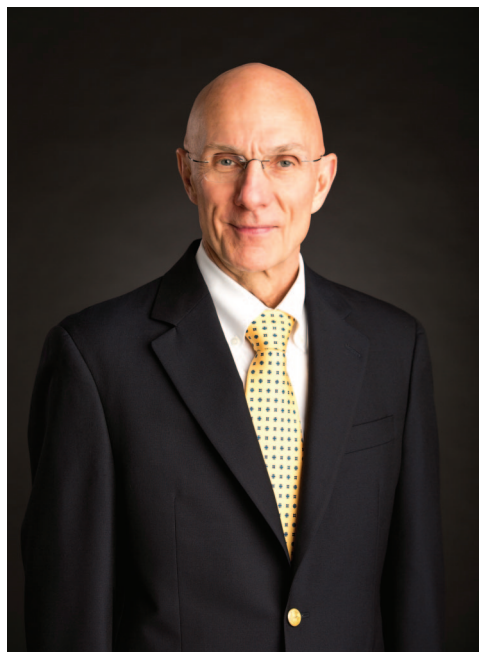
Ralph Lydic, Ph.D., Recipient of the 2012 Excellence in Research Award

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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 acute⁴ and intensive⁵ 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



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from anesthesiologists made clear that the ventilatory response to hypercapnia was depressed during states of anesthesia⁸ 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

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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 neurobiology¹⁶ 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 journals¹⁸ 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 opioids¹⁹⁻²¹ 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 ketamine²⁴ 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, seda-

tion, 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.

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