If you want to know how something works, build it from scratch. With biological systems that self-assemble, this may be out of reach. A powerful alternative is to sketch out the blueprint and/or interfere with the building plan; watch carefully what happens and interpret the outcome with even more care.

Mammals must breathe at birth. The nervous system must generate a rhythmic motor output driving respiratory muscles and then modulate its frequency and patterns of muscle contraction and relaxation to assure an adequate supply of oxygen and removal of carbon dioxide; reflexes that control and protect the lung and upper airway, as well as coordination with swallowing must also work to (near) perfection. Then, as the infant mammal matures, with alternations in body mass, metabolism, lung and muscle mechanics, sleep and wake patterns, the nervous system must adapt, all on the fly with no scheduled down time for changes.

Breathing was one of the first behaviors studied by the earliest bona fide neuroscientists, late in the 18th century. However, the interests of neuroscientists in breathing faded, and studies of breathing became the domain of physiologists mostly interested in the lung and gas exchange. The brain, the engine of breathing, was essentially delegated the role of a black box transforming information about blood gases into a rhythmic pattern of motor activity that pumped the lungs. Starting in the 1950s, neurophysiologists rediscovered breathing as a worthy problem, their technique of choice was nerve and single neuron recordings, mostly from adult cats, then later rats. In 1986, the neonatal rat became a powerful experimental model, as its brainstem and spinal cord could be explanted to a recording chamber, allowing newly developed in vitro techniques to be applied to understanding basic mechanisms for breathing. The in vitro preparations from newborn rodents piqued interest in the developmental neurobiology of breathing, further fueled by the increasing realization of health problems associated with serious developmental disorders of breathing in humans in the early stages of postnatal life. Understanding how the nervous system reliably wired itself in utero to work at birth and matured hand in hand with changes in the lung, respiratory muscles and body size became in interesting and increasing pressing problem.

The present book summarizes the significant, and in many cases, landmark advances in the past decade in exploiting genetics and molecular biology to understand the neural control of breathing. Developmental disorders that show significant abnormalities in breathing include congenital central hypoventilation syndrome (CCHS), Rett syndrome, Prader-Willi syndrome, and sudden infant death syndrome (SIDS). Remarkably, many of these diseases appear associated with mutations in a single gene, CCHS-Phox2B; Rett syndrome-\textit{MECP2}, or multiple genes, each of which may result in a phenotype leading to a similar diagnosis (SIDS). Mouse models with mutations/deletion of these
genes result in phenotypes that in many cases show remarkable resemblance of the human breathing disorders. This allows systematic investigation of the sequelae from gene defect to breathing dysfunction. These disease-related genes are far from being the only ones of interest. The correct wiring and prenatal development of neural circuits generating respiratory rhythm, transforming rhythm into motor pattern, and providing signals related to blood gases and mechanical state of the lung and respiratory muscles requires a complex and delicate orchestration of precisely timed expression of key molecules, particularly transcription factors, guidance molecules, and receptors. Both serendipity and systematic investigation have unveiled numerous genes whose mutation/deletion produce significant changes in breathing in transgenic mice. These genes include those coding for: Krox20, MafB, Bdnf, GAD67, Mash1, Rnx, Nurr1, PACAP, Phox2b. Significant advances in understanding the particular features of the development of the brainstem (such as rhombomeric specification) where the key circuits for rhythm generation, central chemoreception and peripheral chemo- and mechano-receptor afferent processing are located, provide an essential basis for delineating the effects of mutated/deleted genes.

We all breathe differently: patterns of breathing in different states (sleep/wake, exercise) vary, as do responses to hypoxia and hypercapnia. Remarkable progress is being made in understanding the relationship between genetic and phenotypic variance in mice, e.g., GENENETWORK (www.genenetwork.org), and we should be optimistic that before long we will delineate the gene networks responsible for this variability, and the associated mechanisms. In some cases, breathing variability includes serious disorders, such as obstructive sleep apneas (OSA). Widely recognized as a significant health problem in the adult population, OSA, once thought rare in early life, is quite prevalent in infants and older children, and may underlie developmental disorders such as attention deficit hyperactivity disorder (ADHD). To the degree that there is a genetic component, it is likely to involve multiple genes, and tools to get at these genes are becoming increasingly powerful.

While the chapters in this volume represent remarkable progress, we still have a long way to go before we obtain a clear picture of the genetic and developmental neurobiology of breathing and associated diseases, but based on the work here, optimism is appropriate.

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