PETER RICHARD HUTTENLOCHER

FOR THOSE WHO think that success in science must be based on aggressive self-promotion and take-no-prisoners competition, Peter Huttenlocher's well-spent life teaches how critical insights can gently but inexorably shift the axis of an entire scientific field, and spill out beyond their own confines to influence society at large. Huttenlocher, who was the long-time Chief of Pediatric Neurology at the University of Chicago, died of pneumonia in August 2013 after a long struggle with Parkinson's disease. Wonderfully kind but quietly driven and tenacious, Peter defined how the human cerebral cortex generates synapses in huge numbers during the first months of life, and then surprisingly eliminates many of these synapses during subsequent early years just as the child achieves the most important developmental milestones like walking and speech. This idea, that elimination or "pruning," of synapses is as much a part of learning as the addition of synapses, has reached beyond pediatric neurology to influence fields as far-flung as developmental neuroscience, child development, early education, and native language-learning (Fig. 1).

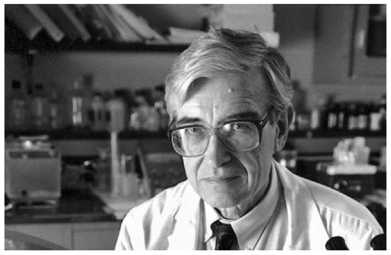

Figure 1 A photo of Peter Huttenlocher taken in his laboratory in 2000.

Peter Richard Huttenlocher was born in Oberlahnstein bei Koblenz, Germany in 1931, and spent his young life in war-torn Germany. His mother, an opera singer, refused to join the Nazi party and fled to the United States in 1937, leaving young Peter and his brothers to be raised in Germany by their chemist father. His experiences as a child witness of Germany during the war, and of the starvation and suffering in the Russian and French zones in postwar Germany, contributed to his lifelong interest in ethics, morals, and human behavior. Peter came to America with his older brother Dieter in 1949 for a visit, but decided to stay. He then attended the University of Buffalo and met his wife and lifelong companion Janellen Burns Huttenlocher, who would go on to become a highly successful cognitive psychologist. Peter graduated *summa cum laude* in Philosophy, and he and Janellen married in 1954 and moved together to Harvard University where she obtained her PhD in Psychology, and Peter received his MD at Harvard Medical School, graduating *magna cum laude* in 1957. After residency training at Boston Children's Hospital and the Massachusetts General Hospital (MGH), he did research fellowships at the National Institutes of Health, where he collaborated with Edward Evarts to perform some of the first electrophysiological recordings of the cerebral cortex of awake cats [1], then at MGH. He was an assistant Professor at Harvard from 1964 to 1966, followed by 8 years at Yale University Medical School. In 1974 he and Janellen moved to the University of Chicago where he was a Professor of Pediatrics and Neurology and the founding Head of Child Neurology, and where he remained for the rest of his career.

In the mid-1970s, Peter started studying the formation of synapses in the brains of normal children and young adults obtained at autopsy. Using electron microscopy and doing much of the work himself, he mapped the arc of synaptogenesis in the cerebral cortex from around the time of birth into adolescence and early adulthood. He originally compared normal brains with the brains of children with intellectual disabilities and was one of the first to observe, along with Dominick Purpura, that synapses in the brain of individuals with intellectual disability tended to be normal in number, but very abnormal in their shape [2]. This discovery of the importance of synaptic shape to normal function is another key element in our understanding of brain plasticity and learning. However, Peter soon discovered that "the findings in the normal population were more interesting than the abnormal population," as he later wrote in an essay on the subject. The number of synapses increased very rapidly during the first year after birth, as might be expected by the need for synaptic connections to form neuronal circuits underlying new abilities and memories formed during that first year. Surprisingly, however, sometime during the second year of life, the total numbers of synapses started decreasing dramatically. He showed that this phenomenon, which came to be called "synaptic

pruning" when it was later discovered in rodents and nonhuman primates, continues over several years, just when children are acquiring language, learning to run, and starting school, with total synaptic counts stabilizing in adolescence [3,4]. His discovery that synapses are normally overproduced and then partially eliminated was 20 years or more ahead of its time, but has gradually permeated most of our ideas of human brain development, from the microscopic (what are the mechanisms that control pruning?) to the macroscopic (what are the possibilities that this synaptic plasticity provides?) to the societal (how do we use our understanding of synaptic development to optimize early educational intervention, early language learning, or early music instruction?). When it comes to synapses, the concept that we must "use it or lose it" has become a touchstone of much of developmental neuroscience over the last three decades. "It would be hard to think of another discovery that is so central to our understanding of pediatric neurology," said his friend and colleague, 2000 Nobel laureate Eric Kandel, the University Professor and Kavli Professor of Brain Science in the Department of Neuroscience at Columbia University and senior investigator at Howard Hughes Medical Institute.

The widely held idea that the early human brain is at its most plastic early on, followed by a progressive restriction of this plasticity as we age, can trace its intellectual lineage to Peter's fundamental insight into synaptic biology, since synapses are the basis of all learning. Over the past decade, most models of autism spectrum disorders suggest that the autistic brain may not lack synapses (since they appear to be at least as numerous as in normal brain) but instead might show defects in the appropriate removal of those synapses that are "normally" eliminated, resulting in a jumble of inappropriately filtered synaptic circuits in the autistic brain. More recently, synaptic pruning has been suggested to be relevant as well for schizophrenia. Peter continued his work on synapses through the 1980s [5]. His contributions to the field culminated in the book entitled "Neural Plasticity: The effects of environment on the development of the cerebral cortex," published in 2002 by Harvard University Press.

Peter also ran a large tuberous sclerosis clinical program, and this allowed him to provide the first genetic analysis of the epileptic brain malformation, periventricular nodular heterotopia, showing that it is an X-linked dominant trait, describing the range of brain and nonbrain findings [6], and collaborating with our lab to identify mutations in *FLNA*, encoding the Filamin A protein, as its cause [7]. This condition should really properly be called the Huttenlocher syndrome because of the definitive nature of his original description. Other contributions included studying MCT oil in the ketogenic diet, the treatment of Reyes syndrome, and his description of Alpers-Huttenlocher syndrome, a remarkable mitochondrial disorder, now known to reflect loss of mitochondrial DNA polymerase γ, manifesting with typically normal development, but then seizures, liver degeneration, and developmental regression. While at Yale, and as Head of the Section of Pediatric Neurology at the University of Chicago, he treated innumerable children with brain disorders and trained a generation of grateful medical students, child neurology residents, and fellows, including Doris Trauner, Elizabeth Berry-Kravis, Frederick Edelman, Carter Snead, Peter Heydemann, Michael Kohrman, and James Tonsgard, among others. His scientific and clinical contributions that helped shape modern pediatric neurology were recognized by the Hower Award from the Child Neurology Society (1984), among others.

Peter remained a person of uncommon balance and perspective, and was known by many as the kindest person you would ever meet. To students like me on his service he was brilliant, yet disarmingly generous and self-effacing. He and Janellen (also deceased, formerly William S. Gray Professor of Psychology at the University of Chicago) raised three healthy and remarkably successful children. His son Daniel is Inaugural Dean of the Schwarzman College of Computing at Massachusetts Institute of Technology, while daughter Anna is Professor of Cell Biology and a pediatric rheumatologist, as well as Director of the MD/PhD training program at the University of Wisconsin and member of the National Academy of Medicine, and son Carl is Chief Investment Officer at Myriad Asset Management, Ltd.); there are also many grandchildren. He enjoyed classical music, the flute, German Expressionist Art, gardening and baking, but clearly enjoyed research, teaching, and caring for his patients above those pursuits. He will be remembered not only for his pioneering and visionary work on human synaptic development, but also by the many patients whose lives

he made better and by the many physicians and students that he so effectively trained in his years at Yale University and University of Chicago.

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