FROM LOSS TO MEMORY

How do the billions of connections between neurons in our brain change as we learn and remember? This is the story of the discovery and the discoverer of synaptic pruning, the process of synapse elimination central to making us who we are. Through Professor Peter Huttenlocher's childhood in wartime and post-war Germany, his emigration to the US to reunite with his mother, and the launch and progressive stages of a career in medicine and research, the motivations and process of scientific discovery that led to an unexpected leap in our understanding of the human brain are uncovered. Accessible examples illustrate how, decades later, researchers are discovering the importance of synaptic pruning in early learning, autism, schizophrenia and Alzheimer's disease.

Physician scientist Anna Huttenlocher is a Professor at University of Wisconsin, Madison and a member of the National Academy of Medicine. Her laboratory studies cell migration in inflammation and cancer. She directed the MD-Ph.D. program at UW-Madison and is a committed mentor to the next generation of physicians and biomedical scientists.

From Loss to Memory

Behind the Discovery of Synaptic Pruning

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For Peter

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PREFACE

This book is the story of the life of Peter Huttenlocher, the pediatric neurologist and physician scientist who discovered synaptic pruning. The book carries interlaced themes – provocative examples of the career path of a physician scientist and the process of scientific discovery, discussion of a surprisingly broad set of social and medical fields that are being impacted by our knowledge of synaptic pruning and a biography of a child of wartime Germany who emerged, through complex twists and turns, to live an engaging life.

I write this book from the perspective of a physician scientist, but also as Peter Huttenlocher's daughter. I would like to acknowledge this inherent bias. Many objective sources were utilized to provide balance in this presentation of Peter Huttenlocher's life and work. The letters and other documents are from Peter Huttenlocher's personal collection. Many of the letters and other documents are translated from German. Other sources include published documents, personal conversations and interviews with neuroscientists and neurologists.

The idea to write this book arose after I attended a conference in Sicily in 2016. My own research focuses on the cell biology of inflammation. The conference was entitled "A Hundred Years of the Phagocyte," in recognition of the "father" of innate immunity, Elie Metchnikoff. At this meeting I was startled to see a slide from my father's 1979 paper first describing synaptic pruning. Professor Beth Stevens (Harvard Medical School) discussed his work as a key inspiration for her subsequent work focused on microglial cells and synaptic pruning. After her talk my puzzled colleagues asked: was that your work on synapses? My response: "Umm ... I was a kid when that work was done – by my father." It is unusual to see decades-old figures presented at current-day scientific conferences. This tends to be done only for truly groundbreaking studies. It made me realize the long-lasting impact of my father's work, and how the significance of these findings had only gained broader recognition in the final years of his life and after his passing. Seeing the work on synaptic pruning presented at a conference 35 years after it was first published – and subsequently learning that his figures are often shown at neuroscience conferences – provided the motivation for writing this book about my father's life and work.

Peter was driven throughout his career to understand how the human brain develops in health and disease. A witness to human atrocity during his childhood in wartime Germany, he also was intrigued by the way the environment influences the development of the human brain during childhood. He took on the old question of "nature versus nurture" during brain development. This question became a particular focus for Peter later in his career, at the end of which he wrote a book entitled *Neural Plasticity: The Effects of Environment on the Development of the Cerebral Cortex* (Harvard University Press, 2002). This is particularly interesting because, throughout much of his life, he hid his own painful childhood memories, even as he worked to understand how the human brain develops and discovered a process, synapse elimination, that is central to the formation of human memory.

The present book is written to make the science accessible. The fields of synapse biology and cognitive neuroscience are broad and exhaustive. The book has been written for a wide-ranging audience and focused on only certain aspects of the field of synaptic pruning, such as recent developments in the area of microglia-mediated synapse elimination. There are multiple exciting areas of neuroscience, which I do not cover, that have significant relevance to synaptic pruning. These include rapid progress in understanding the cell biology of the synapse, the biology of astrocytes, the chemistry of synaptic transmission and work related to synaptic potentiation and depression critical for the formation of human memories. Relevant topics regarding the role of synaptic pruning in medical neurology, psychiatry, psychology and education are discussed. However, the scope of these fields is vast, with many additional areas of rapid and exciting discovery.

My hope is that this telling will be understandable for the student, scientist, physician, psychologist and any persons interested in German history, medicine or science more broadly. This book interweaves science and history to provide insight into the career of a unique pediatric neurologist and cognitive neuroscientist. A number of chapters explore where the discovery of synaptic pruning has taken us four decades later. More centrally, the book tells of the discoverer: the uncommon route through which a child grew into a physician scientist and followed his curiosity to understand the human brain. It is the story of a physician and scientist who, between seeing patients, "dabbled" in the laboratory and, more than once, made fundamental discoveries about how the human brain works.

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