

Autobiography – Thomas C. Südhof

When I was born in Göttingen in 1955, the aftermaths of the second world war were still reverberating. I was born into an anthroposophical family. My maternal grandparents had been early followers for Rudolf Steiner's teaching, and worked for Waldorf schools when Hitler assumed power and banned the anthroposophical movement. Waldorf schools were closed, and my grandfather was conscripted to work in a chemical munitions factory – it was a miracle he survived the war. My uncle was drafted into the army right out of school, and when I was born, he had just returned from the Soviet Union after 10 years as a prisoner of war. My parents were physicians, with my father pursuing a career in academic medicine, while my mother cared for our growing family. My father's training led him to the United States during the time I was born; as a result, he learned of my arrival by telegram as he was learning biochemical methods in San Francisco, where in a twist of fate I now live.

I spent my childhood in Göttingen and Hannover, and graduated from the Hannover Waldorf school in 1975. I had been interested in many different subjects as a student, any subject except sports. I did not know what to do with my life after school, except that I was determined not to serve in the military. More by default than by vocation, I thus decided to enter medical school, which kept all avenues open for a possible career in science or as a practitioner of something useful – being a physician – and allowed me to defer my military service. I studied first in Aachen, the beautiful former capital of Charles the Great, and then transferred to Göttingen, the former scientific center of the Weimar republic, in order to have better access to laboratory training since I became more and more interested in science. Soon after arriving in Göttingen, I decided to join the Dept. of Neurochemistry of Prof. Victor P. Whittaker at the Max-Planck-Institut für biophysikalische Chemie. I was attracted to this department because it focused on biochemical approaches to probe the function of the brain, following up on Whittaker's discovery of synaptosomes in the two preceding decades, his development of methods to purify synaptic vesicles, and his increasing interest in the cell biology of synaptic vesicle exo- and endocytosis. As a lowly 'Hiwi' ('Hilfswissenschaftler' for 'helping scientist') in Whittaker's department, I was assigned the task of examining the biophysical structure of chromaffin granules, which are large secretory vesicles of the adrenal medulla that store catecholamines and ATP. Although my project developed well, I started exploring other questions in parallel as I became more and more familiar with doing experiments, while simultaneously studying medicine at the university. I am infinitely grateful to Victor Whittaker for giving me complete freedom in his department in pursuing whatever I thought was interesting, and continued working in his department after my graduation from medical school and my internship in 1982, until I moved to the US in 1983.

Among the studies I performed during my time in Whittaker's department in Göttingen, the most significant is probably the isolation and characterization of a new family of calcium-binding proteins that we called 'calelectrins' because we had purified them from the electric organ of *Torpedo marmorata*. 'Calelectrins' were among the first identified members of an enigmatic and evolutionarily ancient family of calcium-binding proteins called annexins. Annexins were at the same time discovered in several other laboratories, and I am proud of the fact that we contributed to the first description of this fascinating protein family, although to this date their function remains unknown.

After I finished medical school, I thought that I wanted to be an academic physician, along the mold of my father who had died when I was in high school. Although my time in Whittaker's laboratory had taught me to love doing science, I wanted to do something more practical and immediately useful. The standard career for an academic physician in Germany was to go abroad for a couple of years to acquire more clinically oriented scientific training before starting her/his clinical training. Upon surveying the scientific landscape, I decided to join the laboratory of Mike Brown and Joe Goldstein at the University of Texas Southwestern Medical School in Dallas for postdoctoral training. Brown and Goldstein were already famous for their brilliant cell-biological studies when I made this decision, and were equally renowned for using cutting-edge scientific tools to address a central question in medicine, namely how cholesterol in blood is regulated. While in their laboratory, I cloned the gene encoding the LDL receptor, which taught me molecular biology and opened up genetic analyses of this gene in human patients suffering from atherosclerosis. I also became interested in how expression of the LDL receptor is regulated by cholesterol, and identified a sequence element in the LDL receptor gene called 'SRE' for sterol-regulatory element that mediates the regulation of the LDL receptor expression by cholesterol. Discovery of the SRE later led to the identification of the SRE-binding protein in Brown and Goldstein's laboratory, which in turn identified new mechanisms of transcriptional regulation effected by intramembrane proteolysis.

In 1986, I had the choice of resuming my clinical training, or trying to establish my own laboratory. Much of what I know about science I learned in my three years of postdoctoral training in Brown and Goldstein's laboratory, and has guided me throughout my career. Probably the best advice Brown and Goldstein gave me, however, was now: they suggested I forego further clinical training and do only science, and they backed up this advice by providing me with the opportunity to start my own laboratory at Dallas. This I did, and I ended up staying in Dallas for another 22 years, interrupted only by a short guest appearance as a Max-Planck-Director in Göttingen (see below).

When I started my laboratory at Dallas, I decided to attack a question that was raised by Whittaker's work, but neglected: how do synaptic vesicles undergo exocytosis, i.e., what is the mechanism of neurotransmitter release which underlies all synaptic transmission? In 1986, Whittaker's work had shown that synaptic vesicles could be biochemically purified, but nothing was known about the mechanisms of synaptic vesicle exocytosis in particular, and membrane fusion in general. Our approach, initially performed in close collaboration with Reinhard Jahn whose laboratory at that time had just been set up in Munich, was simple, namely to purify and clone every protein that might conceivably be involved, and worry about their functions later. This approach was more fruitful than I could have hoped for, and has arguably led to a fairly good understanding of membrane fusion and neurotransmitter release. In the 25 years since the start of my laboratory, our work, together with those of others, led to the identification of the key elements of the membrane fusion machinery, to the characterization of the functions of these proteins, to the mechanisms of regulating this machinery, and to the description of synapse-specific molecules that bestow the specific properties of neurotransmitter release onto synapses that render synapses so fast and precise, as required for brain function. Some of the proteins whose function we identified are now household names and have general roles in eukaryotic membrane fusion that go beyond a synaptic function, while other proteins are specific to synapses and account for the exquisite precision and plasticity of these elementary computational elements in brain. I feel fortunate to have stumbled onto this

overarching neuroscience question at a time when it was ready to be addressed, and it has been tremendous fun to work our way through the various synaptic proteins and their properties that shape their functions.

It is important to note, however, that the nature of our studies was not revolutionary. There was not a single major discovery that all at once changed the field, as usually happens for the development of tools (e.g., monoclonal antibodies, patch clamping, or shRNAs, to name a few). The closest our work came to a radical change in the field was probably the identification of synaptotagmins as calcium-sensors for fusion, and of Sec1/Munc18-like proteins (SM-proteins) as genuine membrane fusion proteins, but both hypotheses took more than a decade to become accepted by the field – in fact, the SM-protein hypothesis was only recently adopted by others, 15 years after we proposed it. Thus, our work in parallel with that of Reinhard Jahn, James Rothman, Jose Rizo, Randy Sheckman, Richard Scheller, Cesare Montecucco, Axel Brunger, and many others produced a steady incremental advance that resulted a better understanding of how membranes fuse, one step at a time. As a result of this combined effort, we now know that SNAREs are the fusion catalysts at the synapse, first shown by the discovery that SNAREs are the substrates of clostridial neurotoxins, that SM-proteins in general and Munc18-1 in particular are essential fusion proteins for all membrane fusion events, that a synaptotagmin-based mechanism assisted by complexin underlies nearly all regulation of exocytosis, and that synaptic exocytosis is organized in time and space by an active zone protein scaffold containing RIM and Munc13 proteins as central elements.

Ten years after I started my laboratory, while the work described above was progressing, I was offered the opportunity to return to Germany and to organize a Department of Neuroscience at the Max-Planck-Institut für experimentelle Medizin in Göttingen, my home town. I enthusiastically took on the challenge, planned and oversaw the building of a new animal facility, hired scientists, and organized the renovations and equipment of a suite of laboratories. However, despite of strong local support, it soon became clear that the new leadership of the Max-Planck-Society, which had recently changed, developed doubts about my recruitment, and began rebuilding the institute that I was recruited into in directions that were quite different from what I had been told and what I had envisioned. In a personal discussion, Prof. Markl, then the president of the Max-Planck-Society, suggested I resign my position at the Max-Planck-Institut and look for a future in the US, which I did. I have never regretted my work for the Max-Planck-Institut in Göttingen, which laid the foundation for much of what happened there subsequently, including the recruitment of one of my postdoctoral fellows as a new director who has done a much better job than I could have done. However, I have also never regretted following the suggestion of the president of the Max-Planck-Society, and returning my attention and future to the US, where the breadth and tolerance of the system allowed me to operate in a manner that was more suitable for my somewhat iconoclastic temperament. Overall, my work as a director at the Max-Planck-Institut in Göttingen was a very positive experience that shaped my thinking when I subsequently had the opportunity to help build the Department of Neuroscience at the University of Texas Southwestern Medical Center in Dallas. Contributing to establishing a neuroscience department at Dallas was a lot of fun, and the free-flowing and unbureaucratic environment of a state university was extremely supportive – it was a pleasure to hire young people, and see them develop!

The currently final chapter in my career began when I moved my laboratory from UT Southwestern to Stanford University in 2008. After 10 years as a chair of a Neuroscience Center and then Department in Dallas, I felt that I wanted to devote more of my time to pure science, and to embark on a new professional direction, with an environment that was focused on academics. Moreover, I decided to redirect a large part of my efforts towards a major problem in neuroscience that appeared to be unexplored: how synapses are formed. Thus, in this currently last chapter of my life, I am probing the mechanisms that allow circuits to form in brain, and to form with often near magical properties dictated by the specific features of particular synapses at highly specified positions. I am fascinated by the complexity of this process, which far surpasses the numerical size of the genome, and interested in how disturbances in this process contribute to neuropsychiatric diseases such as autism and schizophrenia. This is what I would like to address in the next few years, hoping to gain at least some interesting insights.

Throughout my career as an independent scientist, I have been generously supported by the Howard Hughes Medical Institute and the National Institute of Mental Health. I am grateful to both for their unflinching support. I have received several recognitions, all of them unexpected, among which I particularly cherish the Alden Spencer Award from Columbia University in 1993, the von Euler Lectureship from the Karolinska Institutet in 2004, and – of course - the Kavli Award in 2010. I am not sure I deserve any of these awards, as conceptual advances in science always represent incremental progress to which many minds contributed. The conceptual advances we made were no different in this regard, they do not constitute a single discovery of a particularly revolutionary method or phenomenon but a continuous postulation and testing of hypotheses. Moreover, our discoveries on how membranes fuse and how calcium regulates fusion would have been impossible without the coincidental findings by others, to whom I am grateful for their contributions. Finally, I feel indebted beyond words to my family, without which I would be barren and rudderless, and which has been more considerate of me than I deserve.