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HOW TO MAKE A NEUROSCIENTIST?

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It happens occasionally, that scientists, neuroscientist included, are "born and not only made". In the majority of cases however the slogan taken from the original and famous Hollywood Maxim, but slightly modified, seems to be more valid: "scientist are not born, they are made".

This was also my case. Before entering the University, at 18, I was hesitating between the profession of my father, who was a very popular country doctor, and the learned profession, i.e. history of our beloved mother. So, although my favorite field was (and is up to the present time) history, I've submitted my application to the Medical Faculty in Budapest. It was 1950, and this explains, that my application did not even reach the Medical School (saying: "we do not want to create medical families"). Instead, the application landed in the Science Faculty of the same (ELTE) University, where suprisingly I was told at the entrance examination, that I will be accepted as a chemistry student. (In fact, I sent immediately a telegram about the "successful" examen to my mother which read: "vegyész lettem" = I became a chemist, which was a little bit misunderstood and sligtly transformed by the postal officer, so that my mother got the telegram: "vegyél meszet" = purchase lime.) However, at the end of August of the same year, and much to my surprise, I've got an official letter, that instead of chemistry in Budapest I'll be a student of biology and chemistry, and not in Budapest, but in the Szeged University.

It turned up, that this change was, in fact, beneficial and decisive about my future possibilities and career – for several reasons. First, the friendly atmosphere, created by the inspirative student companions. Second, and equally important: those outstanding professors, who provided us not only with the necessary knowledge of their topic, but introduced us also to the essence of the University: teaching and research

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as a joint effort. I will mention here only two names, whose lectures were instrumental in directing quite a few of us into science. Professor Sándor Koch, whose brilliant lectures on Crystallography (an otherwise quite boring topic) demonstrated the beauty of the crystalline structures – and the importance of structural details in general. (The memories of these lectures came back frequently when working with the structural aspects of the nervous system.)

Professor Ambrus Ábrahám, who gave lectures on Comparative Anatomy and Physiology for two years. He was especially in his best form when speaking about his own research field: neuroanatomy of the peripheral, sympathetic nervous system. He was full of enthusiasm also, when speaking about the scientific debate of that time, i.e. whether the connection between neurons is contiguous, or (as some German scientists, as well as the famous Hungarian histologist, Apáthy claimed) continuous. Ambrus Ábrahám, at that time (early 50s), in the absence of electron microscope, and using only light microscope, was already on the "right" site, in the noble company of scientists like Ramon y Cajal, Mihály Lenhossék, or János Szentágothai, in stressing (correctly, as later EM studies clearly demonstrated) that, in the neuronal networks the individual neurons are only contacting (by synapse) each other. It was the very popular lectures of Ambrus Ábrahám, which raised in many of us the interest for the study of the nervous system. Following the first, one may say decisive two years in Szeged, I continued my studies for the next three years in Budapest (ELTE), as a student in Biology. Fortunately, I had the good possibility to work on the thesis of diploma in the Physiology Department of the Medical School, in the laboratory of Arisztid Kovách, who knowing my interest in the nervous system, kindly recommended me to János Szentágothai. The big moment came, when Szentágothai offered a junior research position (supported by the Academy) in his Anatomy Department of the Pécs Medical School.

And from this moment a new life began. A new experience in which the belonging to the school of Szentágothai, the happy working hours (from 9 am to 9 pm) of research, – also teaching – and the educative presence of the "old man" (Szentágothai was 43 in 1955 when I arrived to Pécs, but was still the oldest member of the Department), and the feeling of being a member of the "family" were decisive for the future life of all of us. Szentágothai – in addition to being a world famous neuroscientist – was also an outstanding lecturer of Anatomy. No wonder, that he stressed the importance (for all of us in the Department) to teach and to conduct research, jointly. As a consequence, I was teaching also Anatomy (+ Histology, Embryology) for the next couple of decades – both in the eight years in Pécs, and also after moving to Budapest in 1963, the year, when Szentágothai was offered (and accepted) the Chair of Anatomy Department in Budapest).

The eight years, the "learning years" in Pécs were most important to chart a course in future development of a young and unexperienced researcher of functional neuroanatomy. We have learned from Szentágothai some basic principles in science and scientific thinking: "the most important thing is (in contrast to the approach of "let's investigate something for the investigation") to be able to raise meaningful questions, and to try to ansver them". His main, and general question (which was inherited by

all younger members of the school) was: the connection between structure and function of the nervous system – the dependence of function on the structure.

In this context, I was very fortunate to start to work on elementary (later systemic) synaptology. First using light microscopic histochemistry in the study of the huge calyci form synapse in ciliary ganglion, later, with the invent of electron microscopy, the different synapses in the cerebellar cortex, and also in the subcortical visual centre, the Lateral Geniculate Body. In the case of the cerebellar cortex, the question was simple: how is the beautiful, geometric structural organisation realized as function? This was one of the (many) interest of Szentágothai, who made already before the EM age, important discoveries of the morphology of the cerebellar cortex, like the origin of climbing fibers (using experimental approaches) as well as the topographic relation between basket cell processes and Purkinje neurons. (In fact, based on purely light microscopic observations, Szentágothai predicted the inhibitory nature of one of the most spectacular synaptic complex in the cerebellar cortex, the Purkinje basket. This was later confirmed electrophysiologically by John Eccles in Canberra – a starting point of their collaboration and close friendship.) After 1963, I had my "own" Electron Microscope in Budapest, and started to study the ultrastructure of the synaptic connectivity within the cerebellar cortex. This work – in the 60s – resulted in the discovery of the 1. "crossing over synapses", a decisive synaptic system in the operation of the cerebellar cortex, 2. the organisation of inhibitory elements in the complex glomerular synapses, 3. the ultrastructure of the inhibitory Purkinje baskets.

These results were all published in Acta Biologica Hungarica and were later incorporated to the famous book by Eccles, Ito, Szentágothai: "The Cerebellum as a Neuronal Machine". Later, after the introduction of immunocytochemistry in the 80s, using experimental, surgical approach I came to the too early conclusion that, several glutamatergic mossy terminals in the cerebellar glomeruli are not extracerebellar but nucleo-cortical terminals, i.e. they would be coming from the cerebellar nuclei. This interpretation, however, had to be modified quite recently with the discovery of a new cortical, excitatory neuron, the Brush cell, described in 1994 by E. Mugnaini. Due to his work, and also to the results in our laboratory by J. Takács, it is now clear, that many of the "nucleocortical" terminals are, in fact, intracortical axon terminals of this new cell type. Concerning the "crossing over synapses", i.e. synapses between parallel axons and Purkinje dendritic spines, we succeeded to visualize with Tamás Görcs and others, the exact location in the spine synapses of this receptor, which is partly responsible for LTD – type cerebellar learning.

Studies on the synaptic organisation of the subcortical visual centre (LGN), partly in cooperation with the Pasiks in the Mount Sinai School of Medicine (New York) resulted in 1. the morphological identification of the two main afferents (retinal and cortical) and their participation in synaptic circuitry, 2. the morphological identification of the inhibitory GABA-erg local interneuron, 3. the discovery of synaptic triads with the participation of (a) inhibitory presynaptic dendrites, (b) the retinal or cortical axon terminal and (c) the dendrite of the projecting, geniculocortical neuron. Later studies revealed the presence of such triads in other subcortical and brain stem nuclei, spinal cord, and even in cerebellar nuclei indicating the importance of this

structure in information processing. Indeed, the basic architecture of synaptic connectivity within the LGN, including the system of synaptic triads, was later successfully implemented to the analogic CNN (Cellular Neuronal Network programmed by T. Roska), for the simulation of visual processing.

The development and differentiation of neuronal elements, synapses, and networks were from the beginning a topic of research – with many questions and a few answers. The overproduction of nerve cells and processes, a main event in plasticity during development was observed and described already previously (starting with Ramon y Cajal). Our contribution to this plastic process of neuronal differentiation was 1. the demonstration of overproduction of postsynaptic structures, providing the possibility for the use-dependent survival of functionally verified synapses, accompanied by the elimination of not-used "synaptic" structures. 2. Following early functional deprivation (in case of vibrissa-system in rodents) the normal apoptosis of overproduced nerve cells is slowed down. 3. This slowing down of apoptosis was also observed after functional deprivation of vision in the cerebral cortex of cats; however, this process was found reversible. 4. The number of postsynaptic spines during early synaptogenesis is independent of the number of presynaptic axons, and is, therefore, an inherent (genetically programmed) property of the developing neurons. Presently, with József Takács, and other young collaborators, in the Neurobiology Research Group, at the Anatomy Department of the Semmelweis University we are studying the development of cerebellar nerve cells, their place and time of origin during early development, their migration properties and, most importantly, the possibility to induce stem cells located in the wall of the 4th ventricle (the birth place of all inhibitory cerebellar neurons) to produce new nerve cells in the adult.

After this rather long period of a scientific journey – let us try to answer the question again: how to make a neuroscientist? The answer is simple. Obviously, the making needs the conjunction and active presence of helpful scientific stars, who, using their own example can inspire young would be scientists. The second factor in the making was (and hopefully will be) the environment of the education of young researchers: the scientific schools with a friendly, helpful, still competitive atmosphere. The secret of the success of Hungarian neuroscience was always the presence of excellent scientific schools. Schools, where new talents of neuroscience will be born – and made.