Toward the year 2000

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"Panta rhei", everything flows, Heraklid's profound recognition is considered in the natural sciences as the fundamental principle for research. Each research initiative must be based on future orientation as well as the knowledge of continually developing progress. The term progress, often used in modern-day industrial society and often misused is also an essential motivating economical force.

The history of Neurology as a systematic science is quite short and did not begin until the middle of the 19th century. The incidence of neurological illnesses can be traced back thousands of years and we will soon be capable of examining the early stages of man with the help of modern methods of examination on human fossils. It was only recently that the new field of paleoneurology was founded in cooperation with archaeology. The neurological analysis of historical documents and human skeletal remains is being conducted as a second scientific field in Neurology, the history of Neurology. Two new lines of research have thus been established, the paleoneurology and the history of Neurology.

The examination of the mummy of the Tyrolean iceman serves as an example of paleoneurology. The Tyrolean iceman was precisely examined with the aid of modern imaging methods supported by radiological examinations and biopsies. Examination of the mummy revealed that, although he was only 34 years of age upon his death, he had suffered from a number of illnesses. Coxarthrosis

was found in both hip joints as well as massive degeneration of the cervical and the lumbal spine. A lesion in the lower cervical spinal cord discovered with the spinal CT can be explained by the degeneration of intervertebral disks. It seems probable that the iceman, a hunter and gatherer, suffered from cervical myelopathy. Plaques were found in the left internal carotid artery, which had caused a stenosis. The cerebral CT supported the presumption of an brain infarct in the parietotemporal region on the left side. The relatively young man most likely died of a stroke at 3,275 meters above sea level in the Tyrolean mountains due to an infarct in the area supplied by the middle cerebral artery 5000 years ago. (slide 1,2,3)

Aside from reaching a posthumous diagnosis, a new procedure for the reconstruction of the skull and brain from fossils was also developed through the studies on the iceman's mummy. It has been implemented in reconstructed skull bones of australopithecines and skull remains of Homo sapiens neandertalensis. This same reconstruction procedure is used to create skull models to prepare for operations on deformities of the skull. (slide 4, 5)

Research in the field of the history of Neurology depends heavily on the analysis of written documents concerning historical personalities and only seldom has the help of pictorial documentations or sculptures. Meige syndrome serves as an example of pictorial documentation in diagnostic Neurology.

Neurological illnesses have had great impact on world history. Leading personalities of the antique and European history suffered from neurological diseases.

In his book „die Krankheiten der Mächtigen" (The illnesses of the Powerful), Ivan Lesny analyzes eleven historical European figures as to their neurological disturbances. Caligula nicknamed little boots by the legionnaires of his father, Germanicus, successful and popular in his early years as Roman emperor, fell ill with severe encephalitis, most likely herpes encephalitis, at the age of 24. Severe changes in his personality in connection with obvious behavioral disorders developed following his unexpected recovery. His sexual relations with his sister, Drusilla, were a subject of public discussion in the old Rome. As mentioned to these days in history books, the climax of his absurdities was the appointment of his horse as consul, which he declared to put through as replacement for 40 liquidated senators. After he had reigned for 4 years, Caligula was murdered by his own bodyguard. His uncle, Claudius, according to Lesny, had suffered from cerebral palsy with spastic paraparesis of the legs and pseudobulbar paralysis as well as extrapyramidal symptoms. Claudius executed successfully his position as fourth Roman emperor.

Charles IV, Bohemian king and Roman-German emperor about 1350, pulled through a bout of polyradiculoneuritis with almost total tetraplegia around 1350, which had abated after a year's time. Consistent with the time he lived in, the paralysis was believed to have been the result of an attempt of his brother, Johan Heinrich, to poison him, or, according to other sources, due to an overdone love potion from his second wife, Anna. The emperor's severe illness placed great strain on the political stability of Europe. Skeletal examinations of Wallenstein revealed all signs of

tabes dorsalis. Prior to his death, symptoms of progressive paralysis with megalomania was observed. His assassination preceded his certain death due to illness by only a few weeks.

The past century's world history has been influenced by the Parkinson's disease of several leading figures. Adolf Hitler already showed signs of Parkinson's at the age of 50. In the months prior to his death, at which time he was 56 years of age, he was only able to take 20 steps by himself. Evidence suggests that, after the diagnosis of Parkinson's disease by the highest SS–physician, the neurologist De Crinis, became known, the highest ranking of the SS had decided in early 1945 to dispose of him with a specially prepared concoction. Hitler's anancastic personality structure and the symptoms of psychopathy triggered one of the biggest disasters in the history of mankind. Mao Tse Tung, Franco and Breschniew suffered from Parkinson's disease as well.

The neurological analysis of further historical personalities revealed that President Kekkonen had suffered from severe dementia, Stalin died of a stroke, and a cerebrovascular illness led to Lenin's death. Lenin died following his third stroke in acute midbrain and bulbar syndrome. In the USA, there is increasing support for the neuropsychiatric examination of candidates for high-ranking political positions prior to their nomination.

Modern Neurology took its origin in Europe in the middle of the 19th century. In its initial developmental phase, the neurologists focused on the description of typical malfunctions. Several of these neurological illnesses still

bear the name of the neurologists who first described them, such as Charcot's disease and Parkinson's syndrome.

The Viennese psychiatrist Meynert added as scientific conscience neuropathology, the new research field founded to a great extent by him, to Neurology, at that time referred to as neuropsychiatry. In accordance with the law set forth by the Austrian emperor, Franz Josef II, prepared by the private physician of Empress Maria-Theresia, namely the Dutchman van Swieten, every patient in Austria and in some other countries of the former Austro-Hungarian Monarchy who died in hospital was subjected to a post mortem examination. This law is, though in moderate form, still effective in Austria. The imperial decree played a significant role in the elucidation of illnesses of the brain. With his studies, Meynert not only founded neuropathology but also lay the foundation stone for topically based Neurology.

As a result of fundamental studies by the neurologists and psychiatrists of the 19th century and the 2 pathways in the handling of neurological illnesses, two different systems in the study of neurological illnesses have developed. The Neurology of descriptive phenomenology developed as a result of the system of describing the phenomena of neurological of illnesses, whereas the legal obligation to clarify the causes of illnesses of the nervous system led to the topically oriented Neurology of central Europe. Clinical Neurology has, to this day, remained, for the most part, divided into descriptive-phenomenological Neurology and topically based Neurology. It is only now that, with "living pathology" and the help of modern neuroimaging procedures and topical-geographical neurophysiology, this division is being transformed into phenomenological-topical Neurology.

Neurology only slowly managed to gain acceptance as an independent specialty, It wasn't until the end of the 19th century, through the studies of outstanding personalities such as Charcot, Broca, Wernicke, Pick, Babinski, Korsakoff, Wagner von Jauregg, Freud, Alzheimer among others, that the separation of Neurology and psychiatry was finally possible. To this very day internal medicine still tries to maintain its dominant role, as demonstrated by the demand for internist managed stroke units. It is not scientific competence but the interest in the distribution of economic resources which seems to be a driving force.

The overwhelming importance of Neurology is now recognized through the growing knowledge on the wide spread of primary illnesses of the nervous system. Often ignored, is the great number of secondary neurological diseases such as encephalopathy, cervical myelopathy and polyneuropathy, caused by various illnesses of the human organism. Based on rough estimation with consideration given the modern awareness of the regenerative and degenerative plasticity of the brain, one can assume that of all patients 10 to 15% suffer from a primary affection of the nervous system, whereas secondary illnesses of the nervous system caused by other illnesses amount to 20%. This distribution of 30-35% of primary and secondary neurological illnesses can be assumed at an even higher percentage for the past.

Owing to the results of research in biophysics, electrophysiology, biochemistry and pharmacology, a series of specialties arose over the course of the 20th century, such as neurobiochemistry, neurophysiology, neuropharmacology and last of all, modern neuroimaging

methods which took the place of pneumoencephalography etc.

The development in neuropharmacology was influenced substantially by the discovery of catecholamines and their function as neurotransmitters, and the use of neurotransmitter substances in the treatment of neurological and psychiatric illnesses. This led to the development of functional neurobiochemistry and biochemical functional geography of the brain, a new possibility for the topical explanation of neurological illnesses.

Progress in the specialty of clinical neuropharmacology as well as the skyrocketing advances in molecular biology and neurogenetics, new operative methods in neurosurgery and the

functional neurosurgery, in the late 1960's led the integrating field of neuroscience. A powerful scientific community has developed in the field of neuroscience which represents one of the most rapidly growing areas in sciences and justifies the ascertainment from Bloom: "The brain is sometimes referred to as the last frontier of biology".

The initiative to combine the temporary separated neurosciences has arisen from knowledge on the plasticity of the nervous system, neglected in the recent past. The plasticity of the nervous system can be explained with knowledge on its organization.

The nervous system is organized morphologically and functionally, according to a primary principle, established in the brain, the spinal cord and the peripheral nervous system. This primary principle is in constant interaction with internal and external influences. This goes not only

for the normal functioning of the brain but also for pathological changes in the nervous system as well as in the global organism.

The functioning of the nervous system is based on its morpho-logical building blocks and is subject to a hierarchical structuring, according to the level hypothesis of Hughlings Jackson. Details of the functional organization have been of the nervous system are explained, such as the organization of the functional modules of the motor system, from the escape reflexes integrated in the spinal cord to the antigravity reflexes of the midbrain to the limbically coordinated motor patterns and the integration areas of cortical fine motor activity. The various levels of the motor system are tuned with each other in a vertical arrangement.

A functional perspective, supported by Sejnowski and Churchland, differentiates between 5 levels to which a sixth level has to be added.

The lowest level lies at the nano-magnitude of the molecules; the next is the level of the nerve cells the third level, the nerve cells network. An interaction of coordinating network of nerve cells is forming specified cortical map. The brain in its overwhelming functionality has to integrate to select and to control the various specialized brain areas. (slide 6)

The sixth level comprises the functional level of the individual human being in its unique position as a member of its special social organization Specific functions of the different levels are assigned to the individual morphological levels. The molecular level is that of the receptors, the brain cells that of the specific ganglion

cell functions. The nerve cell network is represented by the receptive fields and the expressive fields. The cortical maps are responsible for specific brain functions, such as targeted motoric actions and for the control! of their correct course. The brain carries out complex functions such as differentiated motoric actions and their monitoring as well as the recognition of sensory input. The individual personality is the social competence. Each of the levels has its specific emergent characteristics, which influence the overall dynamics of the system.

A vertical organization tunes the different morphological/ functional levels to each other and subjects these to the objective of the highest brain function.

In the normal development of a human being up until adulthood, the adaptation to the changes in demands in order to be an adult is an essential process. The same goes for damages occurring in the nervous system, or in the rest of the human body for that matter. According to Campbell, biological changes are based on a hierarchy of structural levels, in which each level builds on the level below it. With each step in the hierarchy of biological organization, capacities arise which did not exist at the simple organizational levels. These so-called emergent characteristics result from interactions between components in the form of synergism. Adaptational processes occur on the molecular level. These pertain to the modifications in building of new cell receptors, as well as the modifications in the cell membrane and the mitochondria! structures. Morphological and functional modifications in the ganglion cells and even the glia cells are directly related to these processes. The modification of the synaptic importance, the membrane

excitability, and the production of new synapses serve as a prime example (slide 7).

The synapses are underlying a continuous modeling influence by various activities like peripheral stimulation , behavioral actions but also central stimulation (slide 8).

Besides the remodeling of the synapses there is definite evidence for dynamic modifications in connection with functional demands in adults and mature animals which is proven by the sprouting of dendrites (slide 9) .

The receptive and the expressive fields based on the ganglion cell network are in an anatomic convergence of projective to receptive neurons. There is a physiological dependence of horizontal connections, disinhibition or inhibition and the phenomena of unmasking of synopses (slide 10). The receptive fields and the expressive fields form the cortical maps which represent the actual interface between morphology and function. The cortical maps are morphologically stabile but functionally extremely variable formations, which must adapt to constantly changing environmental conditions by means of neural activation within milliseconds. However, within the normal learning process relatively stable reaction pattern can be built (slide 11).

Lowenstein and Parent in 1999 have mentioned that in the brain of primates including humans, a pool of progenitor cells within the dentate gyrus of the hippocampus continues to produce dentate granule cells throughout life. These newly born cells appear to immigrate throughout the granule cell layer and can extend intricate axon arbors hundreds of micrometers away (slide 12).

Roy et al after their examination with progemtors cell culture stated March 200 that cell substrates could be used for repopulation of damaged or degenerated adult hippocampus in his study on the degeneration and regeneration of the nervous system, Santiago Ramon y Cajal 1913 has postulated that, in the adult nervous system, the nerve paths are something fixed, ended, immobile and everything may die, nothing may be regenerated. However, Cajal observed with prophetic foresight that "it is for the signs of the future to change, if possible, this harsh degree".

The susceptibility and plasticity of the nervous system can be fully utilized therapeutically. Synaptic patterns can be influenced by selective peripheral and central stimulation Hindrance or promotion of certain movement patterns can be used in order to change cortical representation (slide 13).

The enormous progress in neuropharmacology in the past decades can be utilized not only in the progression of illnesses but also for changing an overall malfunctioning system.

The recent program in neuropharmacology brings new implementation for the therapy possibilities like the knowledge about signaling molecules for the mechanisms through which neurons communicate in order to form functional systems. The medicinal treatment of Alzheimer's disease, multiple sclerosis and dementia, as well as the development of new anti-parkinson medications based on peptides, is a general concern of neuropharmacology.

In contrast to conventional pharmacology, gene therapy has brought about the possibility of making the body itself

produce substances through the cells which normally produce or require them. This allows for the optimization of specific effects and the minimization of side effects. Practical results in preclinical research look promising. As regards clinical use, there are still obstacles to be overcome before gene therapy can become a permanent part of the treatment of neurological illnesses. The following slide (slide 14) summarize the requirements for the use of gene therapy in neurological disease.

Conclusively, the topic of reuniting Neurology and Psychiatry, much disputed, in the USA in particular, must be mentioned. In the USA, the dichotomy between the mind and the brain is pointed out by a small group in the field of Psychiatry, whereby the history an the education in both fields, plays a role in this, aside from the still existent supremacy of psychoanalysis in psychiatry.

Representatives of organically based psychiatry, however, point out that the major psychiatric disorders (schizophrenia, mood disorders, panic disorders, etc.) have, by use of PE and functional MRI, been found to actually be illnesses of the brain and that the treatment of such should correlate to that of organic brain disorders.

The duties of Neurology in the years and decades to come are also enormous as new duties arise due to older age in the population. The field of geriatric medicine is currently still an independent specialty, practiced mainly by internists who point out the priority of heart problems.

Neurological complications due to degenerative changes in the skeletal system and the spine in independence to age-dependent illnesses of the nervous system create new

specialties within Clinical Neurology, such as Neuroorthopedia. Neurology has to be aware that a traumatic impact on the skull hits brain and has to be cared by Neurologists. Several new fields must be established and practiced as a means of education.

The duties of Neurology in the coming century have become incredibly diverse. The most intensive training in the field of general Neurology is no longer sufficient; the education of neurologists in the detailed specialties must be planned in time. At the same time a holistic attitude must be maintained. This will be the major challenge of the new century.

Saturday, May 20 2000

18.30 SPECIAL LECTURE

F. GERSTENBRAND (Wien, Austria): Toward the years 2000

19.00 CLOSING CEREMONY

L. BATTISTIN, President of the ESCNP

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