NEUROLOGY – HISTORICAL, RECENT AND FUTURE ASPECTS

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Introduction

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

The incidence of neurologic disorders can be traced back thousands of years. Using modern methods of molecular biology and of imaging, somatic and neurologic disorders of early man can now be studied. Thus, 'paleoneurology' has recently emerged as a new field in which neurologists and archeologists collaborate extensively.

As neurologic diseases have had great impact on the world history, 'historical neurology', i.e. analysis of written documents of contemporaries, personal data, bibliographies, paintings and sculptures of the past, has also become a new exciting field of inquiry in neurology. It obviously bears no relationship to the 'history of neurology'.

Paleoneurology

The examination of the remains of the Tyrolean Iceman (Fig. 1) serves as a good example for paleoneurology. This body was carefully examined using modern imaging methods, supported by radiological techniques and molecular biology studies of biopsy material[1-3].

It was found that, although the man had died in his thirties, he had suffered from a number of illnesses. Coxarthrosis as well as degeneration of the cervical and lumbar spine were pronounced. Stenosis in the lower cervical spine, caused by degeneration of intervertebral disks was detected by spinal CT. It seems possible that the iceman, a hunter and gatherer, suffered from cervical myelopathy. Atherosclerotic plaques in the left internal carotid artery

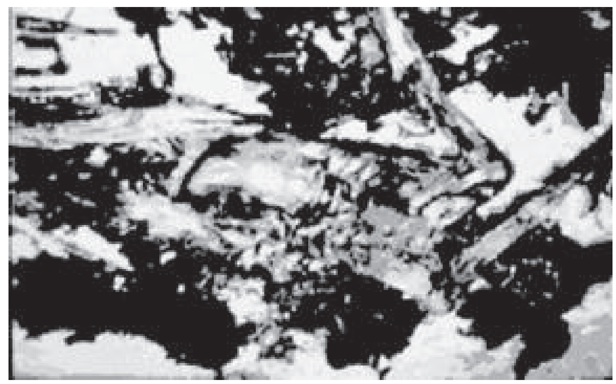

Fig. 1. Tyrolean Iceman mummy (found in 1991 at the Hauslabjoch at 3275 meters)

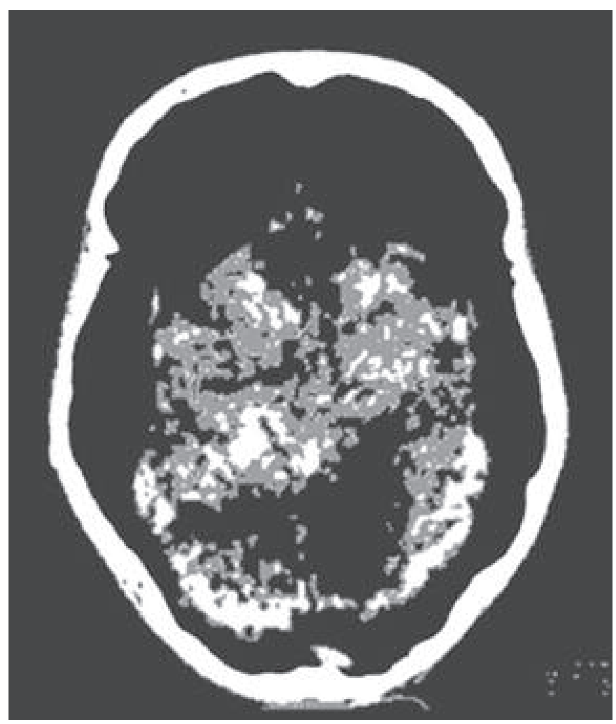

Fig. 2. CT of the Iceman's brain with typical shrinking signs

Fig. 3. Homo sapiens neandertalensis

had caused a stenosis. The cerebral CT supported the presumption of an infarction in the left parietotemporal region. The relatively young man (about 35-40 years of age, correlated to the teeth abrasion) probably died of a left middle cerebral artery - infarction at 3.275 meters above sea level in the Tyrolean mountains between 3350-3500 BC. A reconstruction of the brain indicated typical signs of a shrinking process, seen in ice mummies (Fig. 2). The performance of a brain biopsy was not allowed by the responsible authorities till now. Latest results show that the iceman had been wounded by an arrowhead in his shoulder.

A new procedure in reconstructing the skull and brain from fossils was developed in the course of the studies on the iceman's skull. It has been used in *Australopithecines* and *Homo sapiens neandertalensis*[3,4] (Fig. 3). The same method is used in planning an operation on deformities of the skull[5] (Fig. 4 a,b,c).

Historical Neurology

Because neurologic disorders have had great impact on the world history, the analysis of written documents of contemporaries, personal data, bibliographies, paintings and sculptures of the past, done by neurologists, is a new exciting field in neurology.

Leading personalities of the ancient and more recent European history often suffered from neurologic diseases. In his book "Die Krankheiten der Mächtigen" (The Illnesses of the Powerful), Lesny analyzes eleven leading persons of European history as to their neurologic disturbances[6].

According to Lesny, Caligula nicknamed "little boots" by the legionnaires of his father Germanicus, successful and popular in his early years as Roman emperor, fell ill at the age of 24, with high fever and changes in his state of consciousness. He unexpectely recovered and showed severe changes of his personality[7]. His sexual relation with his sister Drusilla was a subject of public discussion even in old Rome. The climax of his absurdities was the designation of his horse as consul, as replacement for 40 liquidated senators. According to Lesny's analysis, it was most likely herpes encephalitis. After he had reigned for 4 years,

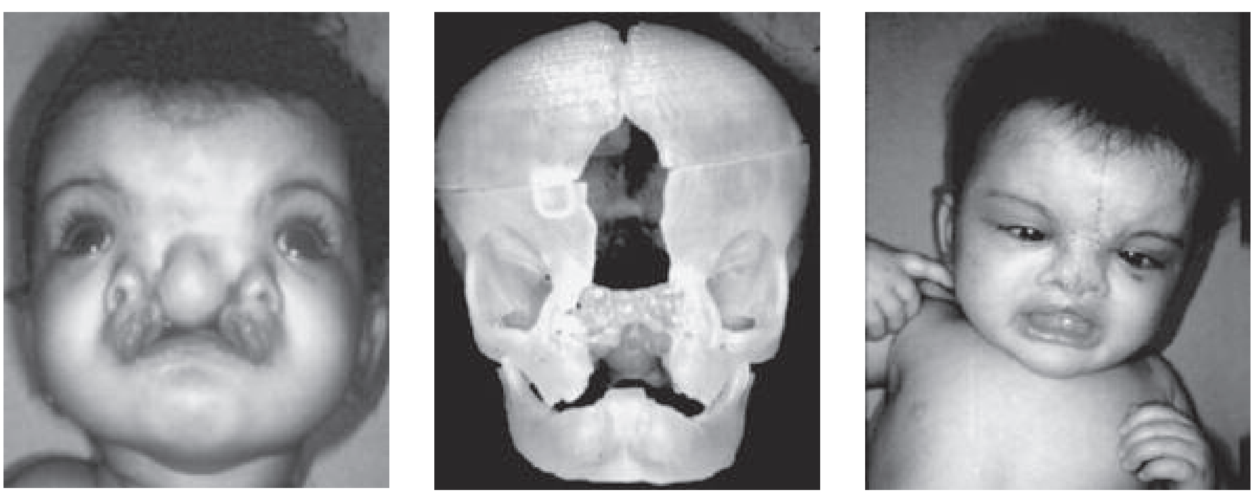

Fig. 4 (a) Preoperative appearance of a girl with a secondary palate cleft; (b) skull reconstruction of the secondary palate cleft; (c) postoperative appearance of the girl with the secondary palate cleft

Caligula was murdered by the tribun Sabinus, an officer of the pretorian guard.

Claudius, the uncle of Caligula and his successor, fourth Roman emperor, was born with cerebral palsy, most likely the dyskinetic type[8]. Analysis of data from that time reveals that his mother might have fallen ill while pregnant and that his birth was 'complicated'. Because of spastic paraparesis of the legs, pseudobulbar paralysis and extrapyramidal symptoms, he was unable to walk and speak normally. Also he had tics orofacially.

Charles IV, Bohemian king and Roman-German emperor in the 14th century, developed an acute almost total tetraplegia around 1350, which had abated after a year's time. Contemporary sources attributed the paralysis to poison, given to him by his brother, Johann Heinrich of Luxemburg, or was supposedly given to him, as a love potion, by his second wife, Anna. Because the illness ran in two attacks, Lesny states that it most probably was a form of polyradiculoneuritis[9]. This would have been the first case of radiculoneuritis in medical history.

Post-mortem examinations on Wallenstein's corpse by the anthropologist[10] revealed all signs of tabes dorsalis[11,12]. Prior to his death, symptoms of progressive paralysis with megalomania were observed. If he would not have been assassinated, he would have probably died of his neurologic disease a few weeks later.

In the past century, many prominent political leaders suffered from neurologic disorders as well.

A cerebrovascular disorder, most likely of the subcortical Binswanger type, led to Lenin's death[13,14]. The course of his illness can be divided into three periods. The symptoms first occurred in March 1922, then again in December 1922 and in March 1923. During a hunting expedition he claimed "my right foot is tired". In March 1922 he had episodes of loss of consciousness followed by numbness of the right side of his body and episodes of speech disturbances. Over the course of a few minutes he was "unable to express his thoughts". These attacks lasted from 20 minutes up to 2 hours. Lenin died after his third stroke with all typical symptoms of an acute midbrain syndrome progressing to a bulbar syndrome[15].

Adolf Hitler showed first signs of Parkinson's disease at the age of 50. In the months prior to his death, he was only able to take 10-20 steps by himself. Analyzing data, the SS physician, neurologist Max De Crinis diagnosed Parkinson's disease in the early 1945 and informed Himmler. Highest ranked of the SS, Schellenberg, De Crinis and Himmler himself decided to give Hitler a special antiparkinsonian concoction, although there was no special antiparkinsonian treatment known at that time. But Hitler's personal physician Stumpfenegger became suspicious and refused to administer it.

The neuropsychiatric analysis of Hitler's personality could lead to a better explanation of the pathological traits of one of the most conspicuous historical personalities[16]. Two different character traits can be analyzed in Hitler's personality, on the one hand the typical premorbid personality of parkinsonian patients, and on the other an antisocial personality disorder with the lack of ethical and social values, a deeply rooted tendency to betray others and to deceive himself, and uncontrollable emotional reactions. This special combination in Hitler's personality resulted in the uncritical conviction of his mission and an enormous drive for recognition.

Mao Tse Tung, Franco, Breshniev, and other leading personalities suffered from Parkinson's disease as well, and also showed signs of typical parkinsonian personality structure with incorrectable mental rigidity, extreme inflexibility and insupportable pedantry. This personality structure influenced their political and ideological program. Typical for Mao Tse Tung is the "long march, passing whole China".

In the USA, there is an increasing support for a change of the twenty-fifth amendment, outlining the transition of power in case of president's disability. Severe presidential disability occurred on October 2, 1919, when President T. Woodrow Wilson sustained a stroke that paralyzed his left side. He was incapacitated for 4 months[17]. President Franklin D. Roosevelt's disability occurred near the end of his life, and the extent of his hypertension was even then known only to a few close associates. His hand often trembled so violently that he could not hold his coffee cup and he spoke with considerable difficulty[18,19]. President Eisenhower's embolic cerebral infarction on September 25, 1957, caused motor aphasia that persisted for some weeks[20].

History of Neurology

The 'history of neurology' as a systematic science was established in the middle of the 19th century. It describes the analysis of historical documents concerning the science of neurologic disorders.

It was not until the end of the 19th century, following the studies of outstanding personalities like Purkinje (Fig. 5), Charcot, Broca, Wernicke, Pick, Meynert, Babinski, Korsakoff, Wagner von Jauregg (Fig. 6), Freud, Alzheimer among others, that separation of Neurology and Psychia-

Fig. 5. Jan Evangelista Purkinje (1787-1869)

try finally took place. Purkinje was the founder of modern neurophysiology. As an admirer, Johann Wolfgang von Goethe wrote a special poem dedicated to him.

Modern neurology took its origin in Europe in the middle of the 19th century. In its initial developmental phase, the neurologists focused on describing typical disorders, where many still bear the name of the neurologists who first described them, like Charcot's disease, Parkinson's disease, and many others. This descriptive neurology, the 'phenomenological' neurology, is mainly the basis of the Angloamerican neurologic schools, constructing a disease but not searching for the structural lesion in the nervous system. Typical examples for this are 'modern disorders' like 'minimal conciousness state' as well as 'vegetative state'.

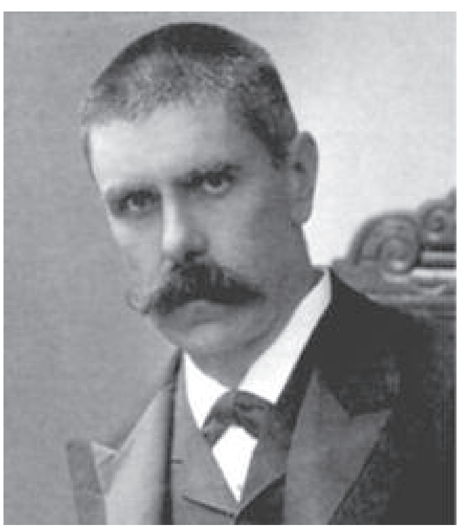

Fig. 6. Julius Wagner von Jauregg (1857-1940)

Franz Joseph II, Austrian emperor between 1848 and 1917, set the law that every patient who died in a hospital of the Austrian-Hungarian empire had to undergo post mortem examination. This decree played a significant role in the elucidation of diseases affecting the brain. Theodor Meynert (Fig. 7), a Viennese psychiatrist, introduced neuropathology as a new scientific field. He founded the 'topically based neurology', which is mainly the basis of the Central European neurologic schools. With 'living neuropathology', named by Grčević[21], based on modern neuroimaging methods and topical-geographical neurophysiology, neuropathology has entered a new phase.

Fig. 7. Theodor Meynert (1833-1898)

Recent Neurologic Problems

The overwhelming importance of neurology is now recognized through the growing knowledge of the wide spread of primary diseases of the nervous system. Often ignored is the great number of secondary neurologic disorders like special forms of encephalopathy, cervical myelopathy and polyneuropathy. Based on rough estimates, one can assume that 10% to 15% of patients suffer from a primary affection of the nervous system, whereas secondary affection of the nervous system is about 20%, often unrecognized and untreated.

Owing to the results of research in biophysics, electrophysiology, biochemistry and pharmacology, a series of specialties evolved in the 20th century, like neurobiochemistry, neurophysiology, neuropharmacology, neurogenetics, neuroimaging, etc. The progress in neuropharmacology was influenced substantially by the discovery of catecholamines, their function as neurotransmitters and their use in the treatment of neurologic and psychiatric disorders[22]. This as well as the skyrocketting advances in molecular biology, neurogenetics, new methods in neurosurgery and in functional neurosurgery together with psychiatry and the basic research in neurology, led in the late 1960s to the integrated field of neuroscience, the platform of modern brain research.

The initiative to combine the temporarily separated different sections of neurosciences has arisen from the knowledge of the plasticity of the nervous system. As a hypothesis of the organization of the nervous system, based on its morphology and functionality, a 5 different level model was created by Sejnowski *et al.*[23].

According to the level hypothesis of H. Jackson[24], the function of the nervous system is based on a hierarchical organization. Details of the functional organization of the nervous system have been elucidated, e.g., organization of the functional modules of the motor system as the lowest, 'withdrawal-reflex' integrated in the spinal cord, the antigravity reflexes in the midbrain centers, the limbically coordinated motor patterns, and the integration areas of cortical motor activity. The various levels of the motor system are tuned with each other in a vertical arrangement.

The functional perspective, supported by Sejnowski *et al.*[23] differentiates between 5 levels to which a sixth level has to be added. The lowest level describes the nanomagnitude of the molecules; the second level the nerve cell itself; the third level the nerve cell network; the fourth depicts the interaction of coordinating networks of nerve cells forming a specific cortical map; and the fifth is the brain itself, in its overwhelming functionality, which integrates, selects and controls the various specialized brain areas. The sixth level, at last, is 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 (Table 1).

Table1. Functional perspectives of the brain organization (modified after Sejnowski, Koch and Churchland)

Level of brain organization	
• Personality	social competence
• Brain	action, recognition
• Cortical maps	dynamics
• Network of ganglion cells	receptive fields
• Ganglion cells	electr. physiol.
• Molecules	receptors, DNA

Table 2. Adaptional processes at the molecular level (Jenkins)

- Cellular mechanism
- Unmasking
- Changing of synaptic strength
- Change of excitability of the cellular membrane
- New synapses

The molecular level is the one of the receptors, the brain cells of the specific ganglion cell functions. The ganglion cell network is represented by receptive and expressive fields. The receptive and expressive fields form the cortical maps that represent the actual interaction between morphology and function. The cortical maps are morphologically stable but functionally extremely variable. They have to adapt to constantly changing environmental conditions by means of neural activation within milliseconds. However, within the normal learning process relatively stable reaction patterns can be built up. They are responsible for specific brain functions, like targeted motor actions and controlling correct course. The brain carries out complex functions, like differentiated motor actions as well as recognizing sensory input. A vertical organization tunes the different morphological/functional levels to each other and projects to the highest centers of brain function.

To achieve mental maturity, adaptation to changes in demands, is an essential process. The same principle applies to damages occurring in the nervous system, or in the rest of the human body.

Adaptional processes occur at the molecular level[25]. They pertain to modifications in building new cell receptors as well as modifications in cell membrane and mitochondrial structures. Morphological and functional modifications in the ganglion cells and even in the glial cells are directly related to these processes. The modification of the membrane excitability, and the production of new synapses serve as a prime example. The synapses are under a continuous modeling influence by various activities like peripheral and central stimulation, but also behavioral actions (Table 2). Besides the remodeling of the synapses there is definite evidence for dynamic modifications, which is proven by sprouting of dendrites[26].

Parent *et al.*[27] found that in the brains of primates, a pool of progenitor cells, in the dentate gyrus of the hippocampus, continue to produce dentate granule cells throughout life. These newly born cells appear to emigrate and built axon arborizations hundreds of micrometers away. Roy *et al.*[28] state, after studying progenitor cell cultures, that cell substrates could be used for repopulation of a damaged or degenerated adult hippocampus.

In contrast, Ramon y Cajal[29] has postulated that in the adult nervous system, the nerve paths are fixed, immobile and that once nerve cells die, they cannot be regenerated. However, he said with prophetic foresight that "it is for the signs of the future to change, if possible, this harsh decree".

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

Recent neuropharmacologic studies have paved the way to new therapeutic strategies. Knowledge about signaling molecules have helped elucidate the mechanisms by which intracellular control of transmitter release and ion channel function are regulated as well as the mechanisms through which neurons communicate in order to form functional systems. The medical treatment of Alzheimer's disease, multiple sclerosis and dementia, as well as the development of new antiparkinsonian medications based on peptides, are a general concern of neuropharmacology.

In contrast to conventional pharmacology, gene therapy has made it possible that cells produce substances, which they require themselves. This allows for optimizing specific effects and minimizing side effects at the same time. Practical results in preclinical research look promising. As to clinical practice, there are still obstacles to overcome before gene therapy can become a permanent part of the treatment of neurologic disorders (Table 3).

Table 3. Gene therapy

- Hereditary damage with known gene defects
- Monogenetic hereditary disturbances, pathogeneses known
- No satisfying conventional option
- Early diagnosis before irreversible damage of neurons
- Direct gene transfer to the involved cells for substitution of the defective gene

Neurorehabilitation

Besides acute care neurology, restorative neurology aimes at neurorehabilitation of chronically ill neurologic patients. Neurorehabilitation was mostly developed after the World War I when hospital wards were filled with large numbers of soldiers with spinal cord injury.

Nowadays for every acute neurologic disorder a specific course of neurorehabilitation is demanded, independent of the severity of the initial damage. This asks for a new system in neurology, based on the knowledge that every acute lesion of the nervous system can be improved or healed. New organizations and institutions have to be built up therefore. A step forward is restorative neurology based on the know-how of regeneration of damaged neural structures using stimulation programs, medications like nerve growth factor, implantation of embryonic tissue as well as deep brain stimulation programs.

In general, rehabilitation has to be divided into acute, temporary and palliative neurorehabilitation. It is a demand that every patient, not only with an acute damage to the central nervous system but also to the peripheral nerves has to be included in a neurorehabilitation program. Patients suffering from chronic neurologic disorders like Parkinson's disease, multiple sclerosis, etc., have to be brought in a temporary neurorehabilitation program. Patients suffering from a noncurable or nontreatable disease such as ALS or malignant brain tumor need palliative neurorehabilitation.

This demand asks for enormous financial support including reorganization of the whole health system. Ethical rules demand that every patient receives the optimal treatment of his or her disease (Helsinki Declaration of 1964)[30].

Ethics

Progress in neurology depends on advanced basic science and on clinical trials. Clinical trials have to fulfill the Helsinki Declaration of 1964 set by the World Medical Association, which determines the "medical conduct in the treatment of the sick person and research on human beings for the development of better medical procedures". Amendments were effected in the process of several revisions, the last one in Edinburgh in October 2000. The use of new medications and the study of their effects is adapted in the rules of Good Clinical Practice – European Union (EU-GCP) and has been regulated in a detailed paper.

The bioethical principles, as they are practiced in the various forms of medical conduct and physician's obligations as well as medical research involving human subjects, have developed with their roots in old Greek philosophy of Socrates, Plato, Aristotle and continued in the teachings of Christian philosophers such as Saint Augustine and Thomas Aquinas[31], precised in the moral philosophy by Kant's categoric imperative. Different ethical rules have been developed in the last century, e.g., existential ethics in France, value ethic - Wertethik in Germany, the Sowiet ethics in Russia, the bioethics in the USA, etc.

Although nowadays there is often a suddenly materializing demand for modern technology, strict observance of the basic principles of human rights has to be done.

The practical application of ethical demands in research projects involving human subjects has been assigned to the responsibility of local ethics committees. A risk-benefit ratio has to be made as well. For every clinical trial the local ethics committee has to give consent. For patients unable to give their informed consent (comatose patients, demented patients, special psychiatric patients, and particularly children), special rules have been established.

Ethical rules of the Buddhist way of life with its counterpart to European progressiveness and the ethics of the Confucianism way of living, with its demand that the wellness of the society has priority over that of the 'individual', have different tasks and cannot be easily brought into line with the doctrine of Occidental bioethics. Still, for the benefit of mankind and man's life in general, as well as to sustain and prolong the life of the individual, Occidental bioethical principles have to accept other cultures and spheres. Currently, it is the other way round, when the principles of 'Ooccidental bioethics' demand the adaptation of the ethical principles of Buddhism and Confucianism without question. Special ethical principles of Islamic and Judaic ethics have to be accepted as well. The task of the 21th century is not only to progress in science but also to harmonize methods of clinical trials and therapies with all the different ethical rules worldwide. Care should be taken that 'evidence-based medicine' (EBM), mostly supported by pharmaceutical grants, remains independent. The historically developed 'experience-based medicine' should not be minimized.

Future Demands

Reuniting Neurology and Psychiatry, much disputed, particularly in the USA, must be discussed. In North America the dichotomy between the mind and the brain is emphasized by a small group in the field of psychiatry. However, representatives of organically based psychiatry point out that the major psychiatric disorders (schizophrenia, mood disorders, panic disorders, etc.) using PET and functional MRI, have been found to actually be disorders of the brain and that the treatment should correlate to that of organic brain disorders.

The tasks of Neurology in the years and decades to come are enormous, as responsibility arises due to aging of the population. The field of geriatric medicine is currently still an independent specialty, practiced mainly by internists. Because it is not only heart failure, blood pressure, etc. to take care of, but mainly cerebrovascular disorders, this specialty should be managed by neurologists.

Due to neurologic complications based on degenerative changes in the vertebral spine, new specialties within clinical neurology, like neuro-orthopedics, are being arising.

'Stroke units', under the care of neurologists, working with internists and neurosurgeons in a team, have been built up in the last years, showing a better outcome for the patients. The specialty of neurointensive medicine and neurotraumatology should be extended as well.

Therefore, 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 one of the major challenges of the new century.

New scientific fields in neurology have to integrate new life-environments such as Space and Orbit, as well as Underwater acquaintances. New research programs are 'Space Neurology' and 'Underwater Neurology'.

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