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Focused Workshops

Sunday, October 27

HIV infections of the nervous system

FW1–1

Opportunistic infections of the nervous system in HIV infection

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Nervous system involvement in HIV infection has become a major issue in AIDS and is due to a spectrum of infective, dysimmune, metabolic, toxic and psychiatric pathogenetic mechanisms. Opportunistic infections of the central (and less frequent, the peripheral) nervous system are present in advanced HIV infection and constitute an important diagnostic and therapeutic challenge. In the era of HAART, prompt diagnosis and rational therapy of such infections become even more critical, since they may affect both quality of life and long-term prognosis. The spectrum of pathogens that can infect the nervous system in AIDS ranges from bacterial, fungal, and parasitic agents to atypical agents and viruses. However, toxoplasma & cytomegalovirus encephalitis, primary central nervous system lymphoma, cryptococcal meningitis, and progressive multifocal leukoencephalopathy are the most common conditions due to opportunistic infections of the CNS in AIDS patients. We will therefore review the clinical features, the diagnosis and the management of opportunistic nervous system disorders in individuals with HIV-1 infection with emphasis on these five conditions. In addition, even when diagnosis seems to be established, the possibility of an additional complication not previously considered or of a new neurological disorder in an HIV patient that has not been previously described should always be considered.

FW1–2

Neuropathology of HIV infections

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In HIV infections, neuropathology has contributed, in addition to diagnostic delineation of opportunistic infections and cerebral lymphomas in AIDS, to our understanding of the specific brain disorders caused by HIV. Their pathogenetic factors have been studied mostly individually in a wide variety of *in vivo* and *in vitro* conditions. While this simple cause-effect approach is our usual way of analysis, it is poorly suited to explain a system as complicated as the action of one of the most complex viruses known, on the by far most complex organ system known, of human beings with distinct genetic individualities and a wide range of medical, ecological, social, and economic environments. Nevertheless, a simplified but unifying analysis is able to recognize three major pathogenetic arms which co-orchestrate a network scenario with distinct neuropathologic sequelae resulting in functional impairment: first, local increase of HIV production manifesting as HIV encephalitis and HIV leukoencephalopathy; second, neurotoxicity of HIV products and/or cytokines, possibly causing diffuse poliodystrophy with neuronal loss; and third, vascular, metabolic and nutritional factors at systemic and local levels, giving rise to vacuolar myelinopathy and angiocentric foci. These three major pathogenetic arms are under mutual influence. The individual case might develop CNS pathology by predominance of one or the other pathogenetic arm, or, more likely, by their combination.

FW1–3

The effects of highly active antiretroviral therapy (HAART) in the brain in different risk groups

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The advent of HAART has resulted in a major change in the treatment and outlook for those individuals living with HIV infection. However, not all individuals with HIV related cognitive impairments improve while taking HAART, and it is being recognised that a significant number of HAART treated individuals have mild cognitive impairments. Cognitive impairments are more common in intravenous drug users who have far higher rates on HIV encephalitis. The enduring cognitive impairments indicate that not all HAART regimes are effective at treating brain resident virus. While some data is accruing as to which antiretrovirals are present in the cerebrospinal fluid, there is very little information as to which are active in the brain. In this talk I will review which brain changes correlate with HIV related cognitive impairments, the noted differences in brain pathology in different risk groups, the approaches that are available to assess antiretroviral action in brain tissue, and our data on the efficacy of nucleoside reverse transcriptase inhibitors.

Selegiline: past, present and future perspectives

FW2–1

The past of monoamine oxidase inhibitors

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Several inhibitors of monoamine oxidase (MAO) were synthesised during the late 50ies and early 60ies in order to develop a potent antidepressive agent. The non-selective MAO inhibitors were effective in the treatment of major depression. However, they induced a life-threatening toxicity called “cheese reaction”. (-)-Deprenyl (selegiline) has been synthesised in the early 60ies

and the first paper about its pharmacological properties was published in 1965 by Knoll and his co-workers. It was proved in 1972 that selegiline is a selective inhibitor of MAO-B, one of the isoform of MAO (Knoll and Magyar). The studies carried out with selegiline revealed that it does not induce cheese reaction, but in a dose needed to inhibit MAO-B does not possess antidepressive action. The first paper regarding the potentiation of levodopa by selegiline was published in 1975 (Birkmayer et al.) and the drug was introduced to treat Parkinson's disease. Based on a retrospective clinical observation Birkmayer and his co-workers firstly published the neuroprotective effect of selegiline in 1985. Selegiline has a dopamine sparing and antioxidant activity. Many studies proved that selegiline pre-treatment protects against the toxicity of the selective neurotoxins. In rather low concentrations it inhibits the apoptosis induced by serum deprivation. Selegiline maintains mitochondrial membrane potential, increases the production of trophic factors, inhibits the metabolism of N-acetyl-polyamines and alters the transcription of more than 50 proteins. Selegiline has an intensive "first pass" metabolism after oral treatment. Studies with selegiline suggest that its effects are shared by the other MAO-B-blockers.

FW2–2

Clinical aspects of MAO-inhibitors with special reference to selegiline

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There is good evidence that selegiline is anti-inflammatory, anti-apoptotic, acts against oxidative stress and combines neuroprotective actions when used in dopaminergic cell culture or animal models. While these data are uniformly accepted, there is still ample hesitation amongst clinicians to consider MAO-B-inhibitors such as selegiline as a neuroprotective agent for patients suffering from Parkinson's disease. In spite of the fact that the DATATOP-study has implicated that selegiline prolongs the time before levodopa has to be added by up to nine months this study is meanwhile not considered to be sufficient proof for neuroprotection. Secondly, the SELEDO-study compared patients with and without selegiline and taking levodopa as major antiparkinsonian agent. The most striking result of this study was the fact that patients taking selegiline needed a much less levodopa dosage-increase than patients without selegiline during a study period of three years. Again this result was considered as a proof for a symptomatic effect of selegiline. In my view the only clinical basis for possible neuroprotection are studies performed by Olanow and Larsen. Both investigators looked for possible neuroprotection by selegiline using different drug regimens. In studies which involved adding or omitting selegiline to either levodopa or the dopamine agonist bromocriptine, for a whole year, Olanow showed that when selegiline was withdrawn during the last month of treatment followed by a week without any treatment, motor symptoms were significantly more reduced in patient who had not received selegiline. Patients who had received selegiline in addition either to levodopa or bromocriptin were much better off than patients without selegiline. The same results were obtained in a more recent study by Larsen's group in Norway. These two studies reflect a possible neuroprotective effect of Selegiline. New MAO-B-inhibitors such as rasagiline may be even more protective. We will discuss the action of Xilopar®, a new formulation which avoids first pass effect in liver and which results in lower metamphetamine and amphetamine blood levels in Parkinsonian patients. The only way to prove neuroprotection in humans will be a study using SPECT or PET methods demonstrating a reduction of cell degradation by use of selegiline. As long as such studies have not been performed in patients, we will not be able to convincingly suggest neuroprotection in human beings by selegiline or other MAO-B-inhibitors.

FW2–3

Neuroprotective and gene related properties of MAO-inhibitors

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Irreversible inhibitors of monoamine oxidase-B (MAO-B) like selegiline and rasagiline show symptomatic properties in humans and exert neuroprotective properties in experimental studies at a dosis, which does not inhibit MAO-B. Molecular biological studies show anti apoptotic properties, increased expression of trophic factors and improved respiratory chain activity. Prevention of caspase 3 activation, increase of Bcl-2 and SOD and PKC activation all have been confirmed by cDNA microarray gene analysis. Nevertheless clinical neuroprotection, e.g. in Parkinson's disease (PD) has not been demonstrated with selegiline. A symptomatic effect could not be excluded due to a half life time (HLT) of around 40 days as assumed from PET derived studies. However recent pharmacological experiments clearly demonstrate a HLT of less than three days. These data are compatible with the suggestion that the beneficial results of selegiline in the DATATOP trial are more likely to be interpreted as being "neuroprotective" while a symptomatic effect is of minor importance.

The role of nuclear proteins in the pathogenesis of different variants of Emery-Dreifuss muscle dystrophy (EDMD)

FW3–1

Clinical phenotypes of X-EDMD and AD-EDMD

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Objectives We would like to present progress of knowledge on Emery-Dreifuss dystrophy (EDMD) transmitted as X-linked or autosomal dominant – AD.
Since the last EFNS workshop (4 years ago) our experience in Emery-Dreifuss dystrophy is much greater and our approach has changed.
Methods and Materials In 47 patients registered in the database (both X-EDMD and AD-EDMD) the following studies were performed: clinical examination, muscle biopsy evaluated by light and electron microscopy and immunohistochemistry, electromyography and biochemistry. In all patients, full cardiological check-ups were performed.
Results We had the possibility to follow the clinical course, i.e. observing increasing myological symptoms and the appearance of cardiac failure in patients observed since their childhood. We have also observed X-EDMD carriers and apparently symptom-free relatives of AD-EDMD patients. Patients with Emery-Dreifuss phenotype, not confirmed genetically, are also periodi-

cally studied to find out whether some of them have proved to belong to another, still unknown variant of EDMD. Both groups of EDMD patients, X-linked and AD, were compared with respect to intra- and interfamilial variability. The intrafamilial variability was more pronounced in the AD form. Aging affects more the progress of cardiac symptoms than muscle weakness and contractures. The X-EDMD carriers sometimes presented very early cardiac symptoms, in no carrier there were any muscle symptoms. LMNA, with a few exceptions, was preserved in emerin-negative X-EDMD cases. A simulation method of motor unit potential made is possible to explain the controversial interpretation in some EDMD cases.

FW3–2

Cardiopathy in X-EDMD and AD-EDMD

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Emery-Dreifuss Muscular Dystrophy (EDMD) is a nucleopathy with three modes of inheritance: X-linked, autosomal dominant and rather rarely, autosomal recessive. The X-linked EDMD, caused by mutations in emerin, is characterized by a cardiomyopathy often presenting as an atrio-ventricular block ranging from prolongation of PQ interval to a complete heart block. The cardiac involvement has been reported to evolve, in the late stage, toward a picture of dilated cardiomyopathy.
The autosomal EDMD, caused by mutation in lamin A/C, has been reported to show three different clinical pictures of cardiac involvement: dilated cardiomyopathy, dilated cardiomyopathy with conduction-system defects, and isolated atrio-ventricular conduction disturbances. However, the studies performed in the last years by acoustic densitometry in the Cardiomyology Section of the 2nd Naples University have shown cardiac fibrosis only at atrial level in almost all patients affected by both X-linked and autosomal EDMD. These findings allow us to foresee that a great percentage of EDMD patients have a tendency to present atrial arrhythmias and blocks but do not support a tendency toward ventricular involvement and consequent dilated cardiomyopathy. This conclusion appears as a main point in the preventive managements in such patients.

FW3–3

The use of skin fibroblasts to study Emery Dreifuss Muscular Dystrophy

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Emery-Dreifuss muscular dystrophy (EDMD) is delineated as a separate form of muscular dystrophy based upon distinctive clinical features. These include early contractures (particularly of Achilles tendons, elbows and the neck), slowly progressing muscle weakness and cardiac conduction defects which are life threatening (reviewed by Emery 2000). At least three forms of the disease have been described including an X-linked form, autosomal dominant forms and a very rare autosomal recessive form. Mutations in the gene STA at Xq28 cause X-EDMD. The gene encodes a 34kDa nuclear membrane protein termed "emerin". In almost all cases emerin mutations result in a null phenotype, although in some instances mutations cause mis-localisation of emerin. Mutations in the gene LMNA cause most forms of AD-EDMD and AR-EDMD. LMNA encodes the nuclear intermediate filament proteins lamin A and C that form part of a filamentous meshwork subjacent to the inner nuclear membrane termed the nuclear lamina. It is not clear how mutations in either protein give rise to this disease phenotype. However, two hypothesise have been proposed recently to explain the diseases. The first hypothesis, termed the structural hypothesis, proposes that weakness of the nuclear envelope leads to its fragility in contractile tissues and that this leads to degeneration of skeletal and cardiac muscle. The second hypothesis, termed the gene expression hypothesis, mutations in emerin and LMNA are both thought to result in altered patterns of gene expression that again promote degeneration in cardiac and skeletal muscle. We have investigated both hypothesise using fibroblast cultures obtained from EDMD patients. Our data suggests that nuclear fragility does indeed occur and this may cause skeletal muscle degeneration. However, in addition altered patterns of expression of important transcription regulators are also observed. Therefore, both nuclear fragility and abnormal transcription regulation are likely to promote the clinical features of the disease.

FW3–4

Muscle ultrastructure in X-EDMD and AD-EDMD

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Objective Two forms of Emery-Dreifuss dystrophy, X-linked (X-EDMD) as well as autosomal dominant (AD-EDMD), are clinically similar. In both the same organelle-myonucleus is affected. The question arises whether the abnormality of the nuclear architecture is identical in both forms of the disease.
Methods Muscle biopsies from both EDMD groups of patients were studied by immunohistochemistry and electron microscopy.
Results In X-EDMD we have shown that the emerin deficiency induces nuclear membrane fragility, disruption and various focal loss of nuclear membrane with nucleoplasm extrusion into the extranuclear space. In addition, proliferation of nuclear pore channels have been observed.
In AD-EDMD – important changes in the chromatin organization have been observed in the nuclei in cases of lamin A/C deficiency. Focal loss of chromatin, rarefaction and paucity of nuclear matrix of various size, and shape, were characteristic for this form. The areas devoid of chromatin sometimes occupied nearly half of the nuclei.
Conclusions Our findings indicate that there are distinct differences in the nuclear architecture in the two forms of EDMD. We suggest that these differences result from the aberrant function of two different proteins.

Advances in drug treatment of metabolic disorders

FW4–1

Enzyme replacement therapy in Fabry disease: Long term safety and efficacy

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Fabry disease is an X-linked lysosomal storage disease resulting from deficient activity of α-galactosidase A (α-GalA) and subsequent accumulation of neutral glycosphingolipids, predominantly globotriaosylceramide (GL-3). Progressive GL-3 deposition, particularly in the vascular endothelium, leads to early demise from renal, cardiac, and cerebrovascular disease. Based on results of a Phase 1/2 clinical trial (Eng et al., 2001, *Am. J. Hum.Genet*. 68:711–722), a Phase 3 multicenter, multinational, double-blind, randomized, placebo-controlled trial was conducted with 58 classically affected patients receiving 1 mg/kg of recombinant human α-GalA (Fabrazyme®, Genzyme Corp.) every 2 weeks for 20 weeks. The accumulated GL-3 was cleared in renal, cardiac, and skin capillary endothelial cells from the treated group (Eng et al., 2001, *NEJM* 345:9–16). GL-3 also was cleared/reduced in other renal and skin cell types. All 58 patients were subsequently treated with Fabrazyme in an ongoing open-label extension study for an additional 18 months. GFR has remained stable after 18–24 months of Fabrazyme treatment; average serum creatinine levels have remained stable and within the normal range during the same period of Fabrazyme treatment. Overall improvement in pain scores, assessed with the Short Form McGill Pain Questionnaire, was sustained throughout the period during which patients received Fabrazyme treatment. As expected, at the 18-month assessments, 52/58 patients (90%) IgG seroconverted; 44/52 (85%) seroconverted within 3 months of Fabrazyme treatment. This rate of early IgG seroconversion has not impacted efficacy: GL-3 reduction was maintained in multiple renal cell types examined by histopathology at up to 12 months of Fabrazyme treatment and plasma GL-3 clearance was sustained during the same period of time. Further, the majority of seroconverted patients demonstrated a four-fold or greater reduction in titer over the 18-month period. Importantly, the frequency of the conservatively managed reactions during infusion has markedly decreased over time, as the rate of administration has increased: after 18 months of open-label treatment with Fabrazyme, 50/58 (86%) patients completed one or more complete infusions of Fabrazyme in ≤2.5 hours, and 35/58 (60%) patients completed one or more complete infusions of Fabrazyme in ≤2.0 hours We conclude that long term therapy with Fabrazyme is safe, well tolerated, reverses the disease pathology, and is clinically beneficial.

FW4–2

Enzyme therapy of Pompe's disease

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On behalf of the Rotterdam studygroup on Pompe's disease:
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Pompe's disease or Glycogen storage disease type II is an autosomal recessive inherited myopathy. Lysosomal glycogen accumulation is caused by alpha-glucosidase deficiency. Patients with the infantile form present with hypertrophic cardiomyopathy and generalized muscle weakness. Milestones like rolling over, sitting and standing are not achieved. Patients die within one year of age. Patients with Late onset forms of Pompe's disease have progressive limb-girdle muscle weakness with involvement of respiratory muscles. There was no treatment until now.

The research of the Rotterdam group has focused on the development of enzyme replacement therapy for Pompe's disease and has led to large-scale production of human recombinant alpha-glucosidase in milk of transgenic rabbits. In a phase II study this therapy was given to four patients with the most severe infantile form of Pompe's disease. Treatment appeared safe and effective (The Lancet 2000; 356: 397-8) The alpha-glucosidase activity in muscle normalized, and all 4 patients are still alive at age 3.5–4 years. One patient learned how to sit, stand and walk.

In parallel, three patients with late onset Pompe's disease received treatment. They were 12, 16 and 32 years old at start. They were all wheelchair bound. The two older patients were ventilator dependent and showed a significant deterioration of pulmonary function before start of treatment. After 2.5–3 years of treatment their pulmonary function has stabilized or improved. The alpha-glucosidase activity in muscle increased. All patients report less fatigue and more energy. The best improvement of muscle strength and function was obtained in the youngest and least affected patient. After 72 weeks of treatment this patient started to walk, having been dependent on a wheelchair for 4 years.

In conclusion, recombinant human alpha-glucosidase from rabbit milk has a positive effect in both infantile and late onset Pompe's disease. There is all reason to continue the development of enzyme replacement therapy, finally to make it possible to treat greater groups of patients.

FW4–3

Treatment of cerebrotendinous xanthomathosis

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Cerebrotendinous xanthomatosis (CTS) is a rare neurometabolic disease clinically characterized by infantile cataract, tendon xanthomas, progressive mental deterioration leading to dementia, epilepsy, peripheral neuropathy, etc due to mutations in the sterol 27-hydroxylase gene (CYP27), with abnormal increase of serum and tissue cholestanol and changes in bile acids.

Drugs involved in bile metabolism have been utilized for treatment of such disorder.

We follow many patients affected by CTX, in the different clinical stages and from different families with different mutations.

Here we report on our experience on the treatment of such disorder by chenodeoxycholic acid, sinvastatin, combination of both, in a long-term follow up of more than 11 years: we describe the drug effect on the clinical, biochemical and neurophysiological parameters and we compare data from the different genotypes. We report also our experience in LDS lipoprotein apheresis in one patient and compare the results with the natural history of the disease. As chenodeoxycholic acid is an orphan drug, no more available as pharmacy product in drugstore, we report our experience in supplying drugs to patients in these years.

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FW4–4

Treatment of metabolic myopathies

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Several disorders of glycogen metabolism affect skeletal muscle and up to now 13 different enzymatic defects have been recognized. Glycolytic disorders and phosphorylase deficiency present as predominant signs exercise intolerance, cramps and myoglobinuria. Infantile acid maltase deficiency is characterized by cardiomegaly. Juvenile and adult acid maltase deficiencies have as major clinical signs limb weakness and respiratory insufficiency. Glycogenosis type II is undergoing a therapeutic trial with recombinant alpha-glucosidase replacement that has demonstrated a good response in the infantile form. Current therapy of adult AMD is nutritional (high protein diet), but a future trial of enzyme replacement is under preparation.
Patients with Lipid Storage Myopathies (LSM) are typified by inhibited beta-oxidation and increased intramyocellular lipid content. Most enzyme defects pertain to fatty acid transport in mitochondria of beta-oxidation such as carnitine palmityl transferase, very long chain acylCoA transferase, trifunctional enzyme, medium and short chain acylCoA transferase. LSM are characterized by muscle weakness, myoglobinuria and exercise intolerance. Primary carnitine deficiency is an autosomal recessive disorder characterized by recurrent hypoketotic hypoglycaemia and cardiomyopathy. A gene encoding for the high affinity carnitine transporter $OCTN_2$ is mutated in these patients. Carnitine supplementation is an efficacious treatment and reverses the dilatative cardiomyopathy.

Clinical and research value of brain SPECT and PET

FW5–1

Value of brain SPECT and PET in the clinical setting

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In the last decade PET and SPECT facilities increased as well as the number of available radiopharmacon. Today visualization of different kinds of metabolism and of receptor binding is possible, using PET quantification can be performed as well. PET and SPECT provide functional imaging, which allows investigation of physiological and pathological conditions in vivo. Functional alterations may precede structural abnormalities or explain symptoms of patients without a morphological equivalent.
Various PET and SPECT studies are performed routinely: investigation of glucose ([^{18}F] FDG) or dopamine metabolism ([^{18}F] FDOPA), amino acid uptake (for example [^{11}C] methionine), and of cerebral blood flow ([^{15}O] H_2O, [^{99m}Tc] HMPAO or ECD)), or the examination of different receptors and reuptake sites ([^{123}I] IBZM and [^{123}I] ß-CIT for the dopaminergic synapse, [^{11}C] flumazenil and [^{123}I] iomazenil for benzodiazepine receptors). Numerous tracers have been developed for research purposes as for example [^{11}C] WAY-100635, binding on 5-HT_{1A} receptors. The main indications of nuclear medicine in neurology are the differential diagnosis of dementia, the preoperative evaluation of epilepsy with respect to focus localization, differential diagnosis of movement disorders, acute and chronic cerebrovascular disease and brain tumours, especially relapses. The interpretation of nuclear medicine studies has to be done by an experienced physician under the aspects of structural imaging and clinical history and neurological symptoms respectively. Only a co-operation between these three fields of medicine can provide useful information with respect to diagnosis, prognosis, therapeutic management and therapy monitoring respectively.

FW5–2

Seizure semiology and ictal SPECT – an application of functional brain imaging

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In the preoperative evaluation of patients with intractable partial seizures the application of brain SPECT is accepted, and perfusion SPECT studies using 99mTc HMPAO or 99mTc ECD as tracers are performed routinely. These SPECT investigations can be done either interictally or during a seizure. In temporal lobe epilepsy (TLE) a correct focus detection (or lateralization) with interictal SPECT will be possible in 60–80%. Excellent results are obtained with ictal SPECT studies in TLE, delineating the epileptic focus in 95%. Concommitant activation of connected brain areas has to be taken into account.
Furthermore the application of ictal SPECT can improve the understanding of seizure spreading and seizure symptomatology. So it was possible to demonstrate that dystonic movement of the upper limb was associated with an increase of cerebral blood flow (CBF) in the contralateral anterior basal ganglia. Patients with complete postictal amnesia showed an CBF increase in mesial temporal cortex on both sides together with CBF decrease in med.frontal and ant.lat.frontal regions. During psychotic states and paranoid symptoms elevated perfusion was found in frontal and temporal regions as well as in the anterior basal ganglia. Visual halluzinations were associated with CBF increase in the occipital lobe. Increased CBF was seen in prefrontal cortex during negative motor seizures. In TLE patients with ictal vomiting demonstrated hyperperfusion in the (nondominant) temporal and occipital lobe simultaneously. In frontal lobe epilepsy contralateral cerebellar activation was described. Summarizing ictal SPECT offers the opportunity to visualize cerebral networks.
References: Podreka 1994, 1995, Mountz 1994, Baumgartner 1999.

FW5–3

Value of brain SPECT in research

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SPECT is an available technique which allows the study of functional (perfusion) and biochemical (neurotransmission) aspects of the living brain in large samples of patients using simple technical approaches in a cost-effective manner. Two main areas of brain SPECT research can be identified: the study of pathophysiological basis of neurological and psychiatric diseases, and the contribution to drug research and development.
The diversity of central nervous system diseases and the still incomplete knowledge of the mechanisms that underlie them have contributed to the success of brain SPECT as a research tool in Neurosciences. The ability of SPECT to detect regional

cerebral blood flow variations in different conditions has favoured the investigation of sensorial, motor and cognitive activities (neuroactivation studies), and central effects of central nervous system drugs (pharmacological challenge), in both the normal and abnormal brain. The study of the density, distribution and degree of occupancy of receptors and transporters by means of neurotransmission SPECT imaging is also useful to identify cerebral abnormalities at a molecular level. Indirect measurements of endogenous neurotransmitter release by means of drug challenges are also feasible. Abnormalities in specific systems have been implicated in the etiopathology of many neurological and psychiatric diseases, and medical drugs are being designed with the aim of counteracting the involved abnormality (e.g. L-Dopa for Parkinson's disease, selective serotonin reuptake inhibitors for depression, antipsychotics for schizophrenia, or anticholinesterasic drugs for Alzheimer's disease). Neurotransmission SPECT imaging is useful for target identification, pharmacokinetic and pharmacodynamic studies, therefore contributing to pharmacological advances in Neuropsychiatry.

Monday, October 28

Genetics of stroke

FW6–1

Genetics of stroke. How can we address the genetic background on a population-based approach?

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A small number of single-gene disorders (i.e. CADASIL, Fabry's disease, MELAS) share ischemic stroke as the main phenotypic expression but the vast majority of stroke cases present with the sporadic form of this disease. Therefore these cases are much more important on a population level. They represent a complex trait in which classical patterns of inheritance cannot be demonstrated. Family studies as well as twin studies in humans and animal model data strongly hint at predisposing genetic factors in stroke.
Linkage paradigms as used in single-gene disorders cannot be used in the genetic analysis of polygenic stroke. Therefore, other lines of investigation have been employed to determine the identity of genes associated with the risk of sporadic stroke: quantitative trait locus mapping in animals, candidate gene association studies, and affected sib-pair analyses.
Since sporadic ischemic stroke comprises a large variety of pathophysiologically defined subtypes the identification of genetic factors is rather difficult. Due to this heterogeneity, information regarding a genetically determined susceptibility for specific subtypes of ischemic stroke is scarce. Several studies are presently under way to determine the genetic background of pathophysiologically defined stroke subtypes. These studies use the candidate gene approach as well as affected sib-pair analyses and will be completed over the next years.
The objectives and the design of these studies as well as their preliminary results will be presented and discussed.

FW6–2

CADASIL and other genetic small vessel diseases of the brain

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Small vessel diseases of the brain (SVDB), characterized by alterations of the walls of small arteries, represent about 30% of causes of stroke and a major cause of dementia.
Hereditary varieties can be grouped in 4 categories: 1) CADASIL and other vascular leukoencephalopathies characterized by subcortical infarcts, dementia, migraine, mood disorders and white-matter involvement. The most frequent is CADASIL, a midadulthood autosomal dominant condition due to Notch3 mutations resulting in major alterations of the smooth muscle cells (SMC) of small vessels. Similar cases exist without Notch3 mutations. CARASIL, reported in Japan differs from CADASIL by a recessive transmission, the presence of extracerebral signs (alopecia, intervertebral disk disease), a younger age of onset, a more severe course and no Notch3 mutations. 2) Autosomal dominant cerebral amyloid angiopathies defined by the presence of amyloid in the small vessel walls are due to mutations of various genes (encoding cystatinC, tranthyretin, amyloid precursor protein) resulting in recurrent lobar haemorrhages, small infarcts, dementia and leukoencephalopathy. 3) hereditary cerebroretinal vasculopathies encompass 3 rare varieties with a possible common locus on chromosome 3. Alterations of the walls of brain and retinal small arteries result in ischemic strokes, vascular retinopathy ± migraine ± dementia ± leukoencephalopathy. 4) Among mitochondrial disorders, MELAS is related to tRNA mutations (80% at base pair 3243) with giant mitochondria in the small arteries wall cells resulting in the occurrence, mostly in children and young adults, of migraine, seizures and ischemic strokes.
These genetic SVDB and their sporadic counterparts account for a large number of stroke and dementia. The understanding of the mechanisms involved should help to develop effective treatments, which are presently lacking.

FW6–3

Genetics of risk factors for stroke

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Over the last few years, there has been an increasing interest in research on the genetic basis of cerebral infarction (CI).
Significant associations have been evidenced between increased risk of CI and polymorphisms in genes coding factors related to:
1) platelet adhesion and aggregation (human platelet membrane glycoproteins: Hpa1, Ibalpha, P-selectin glycoprotein ligand-1, von Willebrand factor),
2) coagulation and fibrinolysis (plasminogen activator inhibitor-1 (PAI-1), beta-fibrinogen),
3) metabolism of homocysteine (MTHFR, 5,10-methylenetetrahydrofolate reductase),
4) renin-angiotensin system (ACE),
5) predisposition to hypertension (G-protein beta3 subunit (GNbeta3)),
6) superoxide generation (PHOX, an essential component of NADPH oxidase).
Because the inflammatory processes (promoted and amplified by cytokines) have also been involved in the pathogenesis of CI,

we attempted to search for the association between cytokines genes variants and CI.
We typed functionally significant: IL1-beta C-511T polymorphism, IL1-alpha G+4845T polymorphism, VNTR IL-1RN polymorphism, IL-6 G-174C polymorphism, and TNF-alpha A308G polymorphism.
Patients with CI carrying of allele-G of the IL-1 alpha gene and allele-C of the IL-1 beta gene significantly more frequently presented TIA (transient ischemic attacks) in history; the genotypes "non carrying" of allele-T of the IL-1 beta gene and allele-2 of the IL-1ra gene were associated with more frequent history of stroke. The lack of allele-A of the TNF-alpha gene and allele-T of IL-1 alpha gene was associated with increased risk of cardioembolism.
Genetic variation in different genes is associated with CI; however, the majority of cases in CI are multifactorial in aetiology. So, genetic influences are likely to be polygenic.
Focused workshop: "Genetics of stroke" Monday, October 28.

Quantitative assessment of neuropathic pain

FW7–1

Qantitative sensory testing in neuropathic pain

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Neuropathic pains are neither linked to aetiology or to site of lesion. So these conditions cannot be separated on basis of this distinction. Irrespective of the heterogeneous nature of neuropathic pains they do have certain characteristics in common: 1) sensory deficit in the painful area, 2) allodynia or hyperalgesia in the painful area, 3) aftersensations, 4) summation of pain and 5) paroxysms of pain. A better understanding on neuropathic pain requires a classification that takes underlying mechanisms into account.
Neuropathic pain has been classified in various ways, but a pathophysiological useful classification distinguishes between: stimulus-dependent and stimulus-independent types of neuropathic pain. The stimulus-dependent types of pains include mechanical and thermal evoked pains, while the stimulus independent types are characterised by spontaneous, ongoing types of pain. In the individual patient the various types of pain may coexist in different combinations and contribute to the heterogeneity of the clinical picture.
Quantitative measures permit a more detailed analysis of sensory function and may be used for subclassifying different types of neuropathic pains. Quantitative sensory tests involve a series of stimuli: mechanical (touch, pressure, pinprick, brushing) thermal (cold and hot) chemical (capsaicin, irritants etc.). These stimuli can be applied either as single or repetitive stimuli to recruit summation phenomena. Responses can be either stimulus dependent (variable stimulus and fixed response e.g. to generate thresholds) or response dependent (fixed stimulus and variable response e.g. to evoke a sensation).
In certain conditions it is possible to demonstrate sensitisation of nociceptors together with dynamic mechanical allodynia, in some the allodynia is present together with a severe loss of c-fibre input, in some there is differential response to different stimulus modalities and yet in others there is pain together with loss of afferent input and loss of allodynia. A combination of these phenomena is likely to be present in many neuropathic pain conditions. By these means it is possible to dissect some of the mechanisms underlying neuropathic pains.
Combination of quantitative sensory tests with pharmacological modulation of neuropathic pain is another way to unravel mechanisms of pain, which may lead to a rational treatment for the individual patient with a neuropathic pain condition. Quantitative sensory testing is tedious, but represent an important step to increase knowledge about neuropathic pains and how to handle them.

FW7–2

Contribution of microneurography to the study of the pathophysiology of neuropathic pain

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Patients with peripheral neuropathy commonly express positive sensory symptoms, such as tactile paresthesias, dysesthesias and pains. As opposed to negative sensory phenomena whose electrophysiological correlate can be readily measured through conventional laboratory methods, the study of positive sensory phenomena relies largely on quantitative psychophysical tests. In animals, possible electrophysiological correlates of positive sensory phenomena have been documented in traumatic neuromas and in demyelinated nerve fibres. In experimental human volunteers, ectopic nerve impulses generated in single myelinated sensory fibres have been correlated with post-ischemic and post-tetanic paresthesias. In patients, abnormal nerve impulse activity in afferent fibres has occasionally been recorded in polyneuropathy, amputation neuroma, and Spurling and Tinel's signs. In all cases, such activity was either spontaneous or elicited by mechanical stimuli applied at injured midaxon level. In addition to spontaneous ectopic activity, generation of abnormal nerve impulses in hyperexcitable myelinated fibres in patients with peripheral neuropathy and positive sensory symptoms has also been recorded.
Recent microneurographic techniques permit recording from individual unmyelinated C fibres and allow their segregation into different functional classes having discrete electrophysiological properties of their membranes. Particularly important for the study of physiological and neuropathic pain is the recording from mechano-sensitive as well as mechano-insensitive, or silent, nociceptors. Recent findings will be presented and their pathophysiological implications or the study of neuropathic pain will be discussed

FW7–3

Nociceptive reflexes and pain evoked potentials

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Pain-related reflexes and evoked potentials are aimed at assessing function of small nociceptive afferents and central pain pathways. So far these methods have not achieved a general consensus about their reliability because electrical stimulations entail the co-activation of large, non-nociceptive afferents. In the central nervous system the large-fibre input contaminates, hinders, or even suppresses nociceptive transmission and pain-related brain signals.

With the introduction of high-power laser stimulators in clinical neurophysiology it is now possible to activate selectively mechano-heat nociceptors innervated by Ad fibres (AMH) or C fibres (CMH) and evoke purely nociceptive reflexes and brain evoked potentials.
Laser evoked potentials (LEPs) following activation of AMH units from the foot, hand, and face are easily recorded and are being widely used to assess nociceptive function in peripheral neuropathies and central lesions. Although these responses yielded reliable information in diabetic neuropathy, small-fibre neuropathies, postherpetic neuralgia, syringomyelia, Wallenberg syndrome, and post-stroke thalamic pain, they do not seem to measure perceived pain.
The recording of C-fibre-related LEPs (which are expectedly more promising in pain syndromes) is far more difficult. Although several experimental studies have been published, the investigators have proposed different techniques and a general agreement on one standard technique is still lacking.
New nociceptive reflexes elicited by laser stimulation of the face, hand, and foot are now being studied in experimental settings. The first results show that these responses correlate with pain perception and are strongly modulated by analgesic drugs and by the central antinociceptive systems.

FW7–4

Functional neuroimaging

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We shall review brain responses to pain assessed through functional imaging techniques (PET/fMRI) and put them in correlation with electrophysiological and clinical data. Functional brain activation is reflected by increases in cerebral blood flow (rCBF) or blood oxygen level dependent (BOLD) signal. CBF increases to noxious stimuli are almost constantly observed in second somatic (SII) and insular regions, and in the anterior cingulate cortex (ACC), and with slightly less consistency in the contralateral thalamus and the primary somatic area (SI). Activation of the lateral thalamus, SI, SII and insula are probably related to the sensory-discriminative aspects of pain processing. SI is activated in roughly half of the studies, its probability of activation being related to the total amount of body surface stimulated. ACC does not seem to be involved in coding stimulus intensity/location, but appears to participate in the affective, attentional and response selection concomitants of pain. Increased rCBF in posterior parietal and prefrontal cortices is thought to reflect attentional and memory networks activated by noxious stimulation. Motor-related areas (striatum, cerebellum, SMA), as well as regions involved in pain control (periaqueductal grey) are also often activated. In patients, chronic spontaneous pain is associated with decreased rCBF in contralateral thalamus, which may be reverted by analgesic procedures. Abnormal pain evoked by innocuous stimuli (allodynia) has been associated with amplification of the thalamic, insular and SII responses, concomitant to a paradoxical CBF decrease in ACC. A number of brain areas activated by acute pain also show increases in rCBF during analgesic procedures. Taken together, these data suggest that haemodynamic responses to pain reflect simultaneously the sensory, cognitive and affective dimensions of pain, and that the same structure may both respond to pain and participate in pain control.

The role of neutralising antibodies to interferon-beta in MS

FW8–1

Evolution, immunological markers, biological and genetic aspects of NAB

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NAB develop mainly during the first year of IFNβ therapy. There is a difference of the incidence of NAB depending on the IFNβ preparation used. Apart from the preparation there are other factors influencing the incidence like manufacturing and purification process, route and frequency of application, and dose. Moreover, a recent study demonstrated a slight but significant influence of the HLA system. The odds ratio to develop NAB was 0.218 in DRB1*11 and 2.636 in DRB5 positive MS patients.
Once NAB have developed they reduce/abolish IFNβ bioactivity. Several reports showing this effect using different – more or less specific – markers (Mx-proteins, beta-2-microglobulin, neopterin, sVCAM) have been published. Also, cellular responses to IFNβ (NK-cells, CD16+ CD3+ cells) revert to pre-treatment levels in NAB positive patients. There are few longitudinal observations of NAB evolution showing that NAB tend to disappear after several years of IFNβ treatment. There appears to be a positive correlation between the NAB titer and duration of NAB presence. In a own series of a small number of patients we found that NAB positive patients with a peak titer of less than 200 neutralizing units (NU) reverted to NAB negative status within 57 months of IFNβ treatment, whereas patients with titers of greater than 200 NU were always NAB positive after 57 months of treatment (average observation time 62 months).
Of all antibodies against IFNβ only a certain proportion account for NAB. The specific characteristics of NAB as opposed to non-NAB are not fully understood. However, there are several lines of evidence that NAB and non-NAB differ in terms of quantitative and qualitative features. NAB positive patients have significantly higher titers of binding antibodies but this does not entirely explain the presence of NAB. IgG isotypes of IFNβ antibodies differ between NAB positive and NAB negative patients and different epitopes on the IFNβ molecule are recognized.

FW8–2

Cross-reaction between neutralising antibodies to Interferon-α2a and Interferon-β1a/-β1b

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Background Human recombinant type I interferons (rIFN-α and rIFN-β) reduce disease activity in multiple sclerosis (MS). However, antibodies to IFN commonly develop during therapy. The antibodies bind to different epitopes of the IFN species and some of these binding antibodies (BAB) are neutralising antibodies (NAB), as measured in anti-viral neutralisation assays. The clinical significance of NAB is still debated, but several studies have shown reduced treatment efficacy in parallel with the appearance of NAB in patients with MS as well other diseases. The presence of NAB also correlates with reduced levels of IFN induced proteins in vivo. Although there are structural differences between rIFN-β1a and rIFN-β1b, NAB to these rIFNs are often cross-reactive, and shift in treatment to alternate β

preparations in NAB positive patients may therefore not be clinically beneficial. In the case of IFN-α, NAB to rIFN-α2a cross-react with other rIFN-α subtypes, but to a lesser extent with natural IFN-α (nIFN-α). Therefore, nIFN-α may induce a secondary treatment response in patients with NAB to rIFN-α.
Method Sera from rIFN-α2a and rIFN-β1a/-β1b-treated MS patients were analysed for NAB cross-reactivity against rIFN-β1a/-β1b and rIFN-α2a, respectively. All sera were analysed in three different laboratories: the laboratory of F. Hoffman-La Roche Ltd., Basel, Switzerland (antiviral neutralisation bioassay – ANB); the laboratory of MediTest GmbH, Lauphein, Germany (myxovirus protein A – MxA induction assay) and the Laboratory for Clinical Interferon Research, Rigshospitalet University Hospital, Copenhagen, Denmark (ANB).
Results None of the NAB-rIFN-α2a positive sera showed detectable cross-reactive NAB against rIFN-β1a or rIFN-β1b. The NAB-rIFN-β1a/-β1b positive sera were cross-reactive, but did not show detectable cross-reactivity against rIFN-α2a.
Conclusion Since cross-reactivity was not found, switching treatment from rIFN-β1a/-β1b to rIFN-α2a, or from rIFN-α2a to rIFN-β1a/ -β1b, might provide a secondary treatment response in NAB positive patients.

FW8–3

Clinical impact of neutralizing interferon-beta antibodies

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Therapy-induced neutralizing antibodies against IFN-beta (NAB) are frequently observed and may interfere with treatment efficacy. In the large clinical trials of IFN-beta in multiple sclerosis (MS), the reported frequencies and clinical impact of anti-IFN-beta NAB vary considerably and seem to depend on depending on the IFN-beta preparation and the assay used for measuring NAB.
In order to evaluate the clinical impact of neutralizing interferon-beta antibodies (NAB) against IFN-beta on the therapeutic efficacy The Danish Multiple Sclerosis Group (DMSG) decided to initiate a study of the occurrence and clinical effect of NAB in all IFN-beta treated patients in Denmark using optimised assays for measuring antibodies binding and neutralizing IFN-beta.
We measured NAB every 6 months for up to 48 months in 422 consecutive MS patients who from 1996 to 1998 started treatment with a commercial IFN-beta preparation. Measurements of NAB were performed in a blinded fashion, using anti-viral neutralization (A549/EMC) bioassays with high (3 LU/ml), medium (10 LU/ml), and low (100 LU/ml) sensitivity and employing different neutralizing capacities as cut-off value for definition of NAB-positive samples.
NAB generally appeared within 12 months after start of treatment and faster with IFN- beta-1b than IFN-beta-1a. However, after 36 months of treatment we observed a significant reduction in the number of NAB-positive patients treated with IFN-beta-1b. The presence of NAB had a significant effect on the relapse rate. During NAB-positive periods, we found a significantly higher relapse rate with odds ratio of 1.55 ($p<0.01$). The time to first relapse in NAB-negative patients was significantly increased by 270 days in Kaplan-Meier analysis of the probability of remaining exacerbation-free ($p=0.028$). Further, we found a trend but no significant effect of the presence of NAB on disease progression measured on EDSS.
Taken together with the results from a number of previous clinical trials, the observations in DMSG study document that the occurrence of NAB reduces the clinical effect. The impact of NAB seems to increase by prolonged therapy. Treatment decisions should still primarily be based on clinical outcome, but in patients with NAB it would be reasonable to substitute treatment if significant clinical activity is observed.

FW8–4

Possible strategies to reduce interferon-beta antibody formation: concomitant treatment with steroids.

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The presence of neutralizing antibodies (NAB) against interferon beta (IFN beta) may occur in treated patients with Multiple Sclerosis (MS) and it has been associated with an attenuation of the therapeutic effect. The biological significance of NAB, however, is not yet completely understood.
To investigate whether the combination IFN beta-1b with steroids should a possible strategy to reduce NAB formation, we examined 161 relapsing-remitting MS patients who were randomised in two treatment arms: a first group (n=81) treated with IFN beta-1b alone (8 MIU every other day), a second one (n=80) treated with IFN beta-1b combined to pulses of intravenous methylprednisolone (MP-1000 mg once a month). Blood samples were analysed at baseline and at month 3, 6, 9, 12 and 15. The titre obtained was defined as serum dilution able to gain inhibition to induce production of the Myxovirus resistence gene-A protein (Mx-A). Positivity was indicated as >20 neutralizing units, limitedly to two criteria: I) one or more non-consecutive NAB+ samples; II) at least two consecutive NAB+ samples. When compared with IFN beta-1b alone, the combination therapy group showed a relative reduction of 54.9% and 52.9% of NAB occurrence according to the I and II definitions, respectively. These data demonstrate that the frequency of NAB formation is considerably reduced by addiction of steroids in a combination treatment.

Complications in the follow up of traumatic brain injury (TBI)

FW9–1

Pharmacologic treatment of fatigue in brain injury

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Neurological disorders produce profound alterations in physical and cognitive stamina. While studies have demonstrated that improved physical conditioning and endurance assist in increasing cognitive endurance, pharmacological methods may also be instituted to reduce fatigue in both acute and chronic neurological disorders. While agents that increase catecholamines (norepinephrine and dopamine) have been the primary intervention for many years, more recently the use of modafinil has been very successful in the treatment of fatigue associated with multiple sclerosis. This presentation will review the differential diagnosis of conditions resulting in fatigue in the general popu-

lation as they relate to the comprehensive evaluation of fatigue in brain injury. Treatment strategies will be discussed based upon a review of the relevant behavioral neuropharmacology of fatigue and engagement. A convenience sample of 64 patients presenting for care at an outpatient neurorehabilitation facility were followed in a 12 week open label trial of modafinil to improve fatigue associated with neurological injury. Results indicate a trend towards diminished fatigue in that population especially in those patients naïve to catecholamine treatment. Further results of the study will be discussed and suggestions for clinical application will be reviewed.

FW9–2

Posttraumatic hydrocephalus

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abstract not received

FW9–3

Traumatic cervical artery dissections

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Dissection of the cervical arteries is one of the most relevant primary traumatic sequelae with high risk of secondary brain lesions (e.g. infarcts, subarachnoidal bleeding). Direct vascular trauma or indirect trauma following cervical flexion and/or rotational trauma lead to intimal disruption and/or flapping of the wall or adventitial disruption followed by local arterial occlusion or arterio-arterial embolisms. Clinical acute or delayed TIA or infarcts are the leading signs and symptoms located in the anterior or vertebro-basilar territory, av-fistulae, pseudoaneurysms at different levels may occur. There are different biomechanical details of the trauma mechanism which may increase the risk of arterial dissections. Clinical, sonographic examinations as well as MRT-techniques for definite diagnostic evaluation are required. The spectrum of dissection patterns, of pseudoaneurysms in the early and late posttraumatic period will be demonstrated, the clinical signs and symptoms presented, and the spontaneous course and the actual lines of treatment will be discussed.

FW9–4

Post-traumatic epilepsy: is prophylactic treatment really efficacious?

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Prophylactic treatment is any therapeutic measure taken to prevent disease, also after its withdrawal. Use of anticonvulsant drugs, as prophylactic treatment for late posttraumatic seizures, remains nowadays controversial. After traumatic brain injury immediate seizures (within 24 hours), early seizures (within 14 days) and late seizures may appear. The ripening of the epileptogenic posttraumatic foci, responsible for late seizures, must be sought in lipid peroxidation activated by iron or heme compounds deriving from blood in contact with cerebral cortex. It has been demonstrated that treatment with anti-epileptic drugs is effective to block the rising of early seizures, but no clinical trial clearly demonstrated an effective role of a prolonged treatment in reducing or blocking late seizures. Prophylaxis, for some Authors being a method that must be started immediately after head injury; is not important for others in the moment in which therapy begun. Finally, many Authors observed that withdrawal of the anticonvulsant therapy effective in blocking the attacks for months was followed by the appearance of seizures. In the present study the Author's personal experience with two series of brain injured patients who received prophylactic anti-epileptic therapy (the first series, 424 patients, in years 1980 and 1990; the second one, 345 patients, in 1992 and 1998) is discussed.
No doubt prophylaxis of early seizures is mandatory in the first days after injury in patients who developed consciousness disturbances. In such cases epileptic activity could give rise to secondary brain injury, due to increase of metabolism, intracranial pressure and neurotransmitter synthesis. Anti-epileptic treatment is able to block early seizures and to control the attacks for months during its administration, but doesn't seem to block the ripening of epileptic foci and late seizures.

History of neurology

FW10–1

Highlights in the history of neurosciences in Austria

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Based on internal medicine and psychiatry, the neurosciences in Austria began to develop during the time of Empress Maria Theresa, e.g. with the description of CNS inflammation in *De nevrosibus* by J. P. Frank (1824) and *phrenology* by F. J. Gall (1745–1823).
Under the influence of the pathologist C Rokitansky (1804–1878), the trio of Viennese neurology – L Türck (1810–1868) as the initiator, Th. v. Meynert (1833–1893) as the activator, and H. Obersteiner (1847–1922) as the founder of the Vienna Neurological Institute, presented basic contributions to the morphology and pathology of the nervous system.
At the end of the nineteenth and in the early twentieth century they were followed by important publications by S. Freud (aphasia), O. Redlich (tabes), E. Streussler (CNS syphilis), A. Spitzer (fibre anatomy of the brain), Schilder (diffuse sclerosis), J. v. Wagner-Jauregg (Nobel price for medicine, 1927), A. Schüller (histiocytosis X), C. v. Economo (encephalitis lethargica; cytoarchitectonics of the cerebral cortex), E. Pollak (Wilson disease), E. Gamper (mesencephalic subject), J. Gerstmann (GSS and Gerstmann syndrome), H. Hoff with L. Schönbauer (brain surgery), and others.
Major research institutions were the departments of Psychiatry I and II, University of Vienna (foundation 1870; unification 1911, separation 1971), the Obersteiner Institute (foundation 1882; separation 1993), the University departments at Graz and Innsbruck, both founded in 1891, and other laboratories where renowned clinicians and neuroscientists, including O. Marburg, H. Hoff, O. Pötzl, O. Kauders, F. Seitelberger, H. Tschabitscher, K. Weingarten, H. Reisner, H. Petsche, F. Gerstenbrand, H. Bernheimer, H. Lassmann, W.-D. Heiss, W. Poewe, L. Deecke and many of their associates produced important contributions to many of the problems of modern neuroscience.
Important for the future are the foundation of the Institute of Brain Research at Vienna University and of the Austrian Society of Neurology which will give great impact for the future neuroscience research in Austria within the framework of the European Union.

FW10–2

Todd, Hughlings Jackson and the electrical basis of epilepsy

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John Hughlings Jackson is widely credited with the first electrical theory of epilepsy (1873), which was confirmed by the experimental studies of Hitzig and Ferrier. His views are summarised in his famous Lumleian lectures to the Royal College of Physicians in 1890.
Robert Bentley Todd, however, had earlier developed an electrical theory of epilepsy, which he presented in his own brilliant Lumleian lectures to the Royal College of Physicians in 1849. Todd was influenced by the electrical discoveries of his contemporary, Michael Faraday, and thought of the brain as having battery-like properties that led to the sudden discharge of electrical energy (nervous force) in epilepsy.
Unlike Hughlings Jackson, Todd was an anatomist and physiologist as well as a physician, and he did his own electrical experiments in rabbits to prove his theory, something Hughlings Jackson, who relied on Ferrier for scientific and experimental support, could never have done.
There is no mention of Todd's Lumleian lectures in Hughlings Jackson's later lectures and writings, nor in those of Hitzig or Ferrier. Todd's remarkable observations and lectures, and his electrical theory of epilepsy deserve to be drawn to the attention of the medical and scientific community.

FW10–3

Encephalitis

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abstract not received

FW10–4

Haskovec and Pelnar, the Founders of Czech neurology in Austria and Hungary

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Ladislav Haskovec (1866–1944) was one of the last of Charcot's pupils at La Salpêtrière in Paris.
In 1896 Haskovec became the first Docent (Associate Professor) of Neuropathology at Prague Medical Faculty and, reportedly, in the whole of the Austrian Hungarian Empire (the Czech Kingdom was part of Austria-Hungary until 1918). Haskovec's name is connected with the term akathisia that he pioneered in 1902. He also first described gluteal and pilomotor reflexes and he wrote over 100 scientific articles and several chapters in French neurological textbooks. In 1904, he founded the Czech journal Revue in Neurology and Psychiatry that was followed by two still existing separate journals.
In 1919, he was named Professor of Neurology at Charles University in Prague and he set up the first University Department of Neurology in Czechoslovakia. During the whole of his life Haskovec was struggling to establish neurology as a distinct specialty, separate from internal medicine and psychiatry. He was respected internationally, an Honorary Member of many national and international societies, and he kept friendly contacts with the greatest neurologists of his time including Bechterev, Déjerine, Marie and many others.
Haskovec was decorated by the Order of Franz-Joseph I and, for his contribution to French neurology; he was awarded the Order of Légion d'Honneur. However, due to unfavourable circumstances he never made real his dream to create in Prague a neurological institution similar to La Salpêtrière.
Josef Pelnar (1872–1964), Professor of Internal Medicine at Charles University in Prague, was deeply interested in basal ganglia disorders and wrote the first modern monograph on tremor (Das Zittern, Springer, Berlin, 1913) as cited by, among others, Macdonald.Critchley. Pelnar represented the second root of Czech Neurology issuing from internal medicine. In 1919, he co-founded the Purkyne Society for the Study of Mind and Nervous System that later developed into the Czech Medical Society.

FW10–5

Neurological diseases may have strangled the German Baroque Music

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abstract not received

FW10-6

A film history of the International League Against Epilepsy

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At the occasion of the ninetieth anniversary of the International League Aainst Epilepsy its history was recorded in a book. In order to present the contents of this book to an audience of 4000 participants attending the 23rd International Epilepsy Congress (Prague 1999) a film of about half an hour was created. The film summarizes the history of the ILAE and its journal Epilepsia in almost poetic images and in addition all members of the Executive Committee 1997–2001 succinctly express their views about the future of the ILAE, Epilepsia and epileptology.

Immunology and neurodegenerative processes

FW11–1

Microglial activation and neurodegenerative disease

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Microglia are normally quiescent, mesoderm-derived brain macrophages and represent the resident immunocompetent cells of the CNS. Rapid local activation of microglia can occur without the lymphocytic infiltrations. This observation has lead to the concept of "neuroinflammation" in a variety of primarily non-inflammatory neurological condition, including neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD).
We briefly outline the rational for employing positron emission tomography (PET) using the ligand [^{11}C](*R*)-PK11195 which binds with relative cellular selectivity to activated microglia in order to detect *in vivo* neuroinflammatory changes in neurodegenerative diseases. In our [^{11}C](*R*)-PK11195 PET study per-

formed in a group of AD patients with mild to moderate disease, increased signals were measured in the temporal cortex, the inferior parietal cortex, the posterior cingulate and the amygdala. In addition, we were able do demonstrate that areas with high PK11195 signals subsequently underwent the most marked atrophic changes within the following year as shown by a longitudinal serial volumetric MRI scans. The patient with minimal cognitive impairment (defined as isolated objective memory impairment) included in our study showed an increased PK11195 binding in subregions of the temporal lobe similarly to those found in AD patients but not in the inferior parietal lobe.
Activated microglia are also seen in the basal ganglia and brainstem nuclei of patients with PD and multiple system atrophy (MSA). Increased [^{11}C](*R*)-PK11195 binding in the substantia nigra and the globus pallidus has been measured in PD patients while MSA patients show more widespread increases in PK11195 binding including nigra, pons, pallidum, caudate, putamen and dorsolateral prefrontal cortex.

FW11–2

Complement and neurodegeneration

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abstract not received

FW11–3

Microglial involvement in chronic neurodegeneration

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The inflammatory response in chronic neurodegenerative diseases is dominated almost exclusively by cells of the mononuclear phagocyte lineage, which is a highly unusual form of inflammation. We have studied murine prion disease as a laboratory model of chronic neurodegeneration, because it has obvious similarities to CJD in man and the many pathological similarities with diseases such as Alzheimer's disease. We have shown that in the terminal stages of prion disease the inflammatory cytokine profile in the brain is dominated by the presence of TGFb1 and PGE_2 while pro-inflammatory cytokines such as IL-1b, TNFa, IL-6 and iNOS are absent. This profile is very similar to that associated with macrophages phagocytosing neutrophils that have undergone apoptosis. At earlier stages of disease, prior to the onset of degeneration of the neuronal cell bodies, synapses degenerate and the animals develop subtle behavioural deficits that are associated with phenotypic alterations of the microglia, synaptic loss and the axon degeneration. The microglia, although they appear morphologically activated, have a similar cytokine profile to that seen at end stage disease. Thus, at all stages of the evolution of the disease the microglia have a profile typically associated with the phagocytosis of apoptotic cells. These microglia are, however, primed either by the deposition of PrPsc or the degenerating neuronal processes. Peripheral challenge with endotoxin (LPS), to mimic a peripheral infection, leads to exaggerated sickness behaviour and enhanced cytokine synthesis in the CNS. These results suggest that peripheral infection and further activation of microglia may contribute to the progression of chronic neurodegenerative disease.

Tuesday, October 29

Motor function and dysfunction: assessment with functional imaging

FW12–1

Motor dysfunction in multiple sclerosis and other white matter disorders: assessment with MR

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Several neuropathological and imaging studies have shown that neuro-axonal damage is relevant in multiple sclerosis (MS) and other demyelinating or dysmyelinating disorders. Axonal transsection and damage in these diseases suggests that neurodegeneration may be an important cause of clinical dysfunction in pa-tients affect by these disorders. Recently, functional magnetic resonance imaging (fMRI) has been used by several research groups to demonstrate that cortical functional reorganization may contribute to limiting disability with progressive irreversible injury from MS. Consistently, fMRI studies (after administration of simple sensory-motor tasks) have altered patterns of brain activation in patients with MS even in the very early stages of the disease. Similar findings are found in patients with other WM disorders such as CADASIL. It has been possible to demonstrate that this cortical reorganization is greater with increasing axonal injury, consistent with an adaptive role for these functional changes. These data suggest that in the initial disease stages, adaptive cortical reorganization may allow complete functional compensation so that the effects of neuronal degeneration remain subclinical. However, this intrinsic adaptive capacity is limited. Development of permanent disability occurs when a threshold of axonal loss is reached and compensatory resources of the CNS are exhausted. Preliminary results suggests that fMRI studies can monitor this process and that this might be a valuable tool to follow pathophysiological cerebral reorganization in MS and other WM disorders.

FW12–2

Motor and language recovery using PET, fMRI and DTI-MRI

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In recent years, functional imaging techniques like functional magnetic resonance imaging, positron emission tomography and transcranial magnetic stimulation have shown that the improvement of motor and language function after ischemic stroke is accompanied by extensive reorganisational changes in the human cortex. The application of these techniques has generated the following findings and hypotheses currently under investigation:
The pattern of reorganisation is highly variable and individually determined. Activation after stroke comprises infarct rim activity or activation of remaining tissue in the original area of representation, as well a shift to neighbouring representations. Extensive use of higher order processing areas, contralateral regions and compensatory mechanisms.
Training, rehabilitation and the administration of drugs do influence recovery and concomitant reorganisation.

Recovery may differ from normal learning in a temporary increase of focal brain excitability, which consecutively returns to normal when the brain has learned to use the alternate routes. This may be the result of an increase in effective connectivity.
We see stroke mostly as a disconnection phenomenon. There is no single "recovery-area". Recovery means recoordination of the remaining parts of the original network. Parts, all of which may play a role in the execution of a certain function but require the coherent support of the others to effect a high level of proficiency.
Diffusion tensor imaging emerges as a new tool to map the connections in the brain, which may help explain not only the constituent parts of the recovery network but also explain symptoms in the presence of subcortical lesions.

FW12–3

Pharmacological modulation of motor cortex activity

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abstract not received

FW12–4

Recovery of motor functions after subcortical stroke: longitudinal PET studies

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In patients recovered from subcortical stroke, PET and fMRI of simple motor tasks have documented reorganisation of cortical maps and neural networks, representing adult brain plasticity. Displacement of ipsilesional primary motor cortex (M1) activation peak may reflect "unmasking" or disinhibition of pre-existing connections, or "recruitment" of neurons/connections normally not devoted to this function. Activation of unaffected-side M1 may represent recruitment of the direct (uncrossed) corticospinal tract and thus relate to mirror movements, but may also reflect bi-hemispheric co-operation as observed with complex tasks in healthy subjects. Excessive activation of ipsilesional M1 and bilateral secondary motor areas may represent over-recruitment of deafferented cortical fields to compensate for the cortico-spinal lesion. Finally, activation of areas normally not engaged in motor tasks might reflect the implication of compensatory cognitive strategies. However, there is no evidence that any of these changes is beneficial to recovery of function. Longitudinal studies performed during the recovery phase have documented significant displacement over time of ipsilesional M1 peak activation but this did not correlate with recovery of measured motor performance. Also observed were i) a decrease in total amount of activated voxels in both hemispheres, and ii) a shift of activation balance between the affected and unaffected hemispheres. There was a significant correlation between the latter and concomitant motor recovery, suggesting recovery is worse when non-affected M1 activation takes pre-eminence over time. Thus, late contralesional M1 activation appears less efficient than ipsilesional activation for recovery, in agreement with some TMS studies. Thus, enhancing the use of the deafferented M1 cortex with e.g. active rehabilitation and/or monoamines should foster recovery.

Use and abuse of intravenous immunoglobulin

FW13–1

Intravenous immunoglobulin (IVIg) in those neurological conditions in which IVIg is of proven benefit

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Intravenous immunoglobulin (IVIg) was shown to be effective in several randomised controlled trials (RCT) in various neurological disorders. The first disease in which a favourable effect was shown, is the Guillain-Barré syndrome (GBS). Additionally, IVIg was shown to be effective in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN) and in dermatomyositis. One trial in patients with myasthenia gravis showed an equal effect of IVIg when compared to plasma exchange. In patients with relapsing-remitting multiple sclerosis (MS), it was shown that IVIg reduces the number of relapses.
Recently, Cochrane reviews in GBS and CIDP showed the favourable effect of IVIg. Nowadays, IVIg has become an important therapeutic option in the treatment of immune-mediated neuropathies. Most patients with CIDP and MMN need long-term treatment, suggesting that IVIg suppresses disease activity rather than cures the disease. IVIg has several advantages compared to other treatment options since it is widely available and the side-effect profile is good. It is, however, a very expensive treatment. The cost and long-term side effects have to be weighted against more cheap drugs like steroids. In MMN there seems to be no good alternative treatment yet, especially since patients with this chronic disorder do not improve to corticosteroids, and other drugs like cyclophosphamide are toxic. In GBS, a recent RCT studied the combination of IVIg with methylprednisolone. New trials in chronic disorders should now also study the effect of treatment during a longer follow-up peroid.

FW13–2

Abuse of intravenous immunoglobulin: Conditions in which IVIG is of marginal or unproven value and including side effects

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During recent years high dose intravenous immunoglobulin (IVIG) is increasingly used as treatment for immune-mediated neurological diseases. IVIG has been used not only for diseases in which clinical effect has been shown in controlled trials, but also for conditions in which IVIG is of marginal or unproven value diseases.
Generally, IVIG therapy is considered safe although side effects are reported in 1–15% of patients treated, and with high single doses of IVIG more than 50% of the patients reported one or more adverse events. Important severe adverse effects are acute renal failure, aseptic meningitis, eczema, and thromboembolic events. Transmission of infectious agents is still a potential danger, although the risk of acquiring hepatitis C probably has been eliminated by new virus inactivation processes.

A beneficial effect of IVIG has been shown in controlled trials in Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy, severe myasthenia gravis, Eaton-Lambert syndrome, inflammatory myopathies, and relapsing-remitting multiple sclerosis (RRMS). However, only in Guillain-Barré syndrome, multifocal motor neuropathy, and Eaton-Lambert syndrome IVIG should routinely be the first choice. In CIDP, IVIG can be regarded as a first-line treatment and a valuable alternative to corticosteroids and plasma exchange with fewer long-term side effects. Further, IVIG should be tried in patients with dermatomyositis resistant to corticosteroids. In severe acute myasthenia gravis IVIG is probably as effective as plasma exchange. Although IVIG has been proven effective in RRMS, it is still only a second-line therapy to the approved immunomodulatory drugs, but can be justified in patients who do not tolerate the approved therapies or are unwilling to perform frequent subcutaneous or intramuscular injections.

In other conditions, including inclusion body myositis, paraneoplastic syndromes associated with antineural antibodies, motor neuron disease with anti-GM1, lumbosacral plexopathy, Isaacs' syndrome, adrenoleukodystrophy, childhood epilepsy, and chronic fatigue syndrome, the use of IVIG can only be considered exploratory or may even be hazardous, and routine prescription in these conditions is unwarranted.

The use of IVIG should be evidence based on proved efficacy in controlled, double-blind clinical trials, and further, the existence alternative treatments, adverse effects and even the cost of treatment and problems of IVIG supply have also to be taken into consideration before IVIG is chosen as therapy for a neurological disorder.

FW13–3

Cost-benefit analysis of the use of intravenous immunoglobulin

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It is important to consider the economic along with the clinical implications of using IVIg to treat neurological conditions. Health care resources are limited and, therefore, it is essential to allocate those resources in an efficient and equitable way. An understanding of the economics of IVIg is even more pronounced given that there are constraints on its supply and potentially many conditions for which it can be used. However, any findings on the costs of IVIg must be combined with information on outcomes. Economic evaluation is not about determining which interventions cost the least, rather it is concerned with maximising effects from a given level of resource use. To date there have been very few published cost-effectiveness analyses of the use of IVIg for neurological conditions. This presentation will summarise the evidence that does exist on the cost-effectiveness of IVIg in the treatment of peripheral nerve disorders. The economic component of recent randomised controlled trial of IVIg compared to prednisolone for CIDP will be used to illustrate the way in which health economics can be used alongside clinical evaluations.

Neuropsychological syndromes in acute stroke

FW14–1

Overview of neurobehavioural syndromes in acute stroke

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Neurobehavioural syndromes are a frequent and often early manifestation of acute stroke, they may complicate its course, are usually associated with an increased risk of unfavourable outcome and may be difficult to manage. This presentation will deal with delirium, denial, depressive symptoms including catastrophic reaction and suicidal thoughts, hallucinations and other perceptual disturbances, maniac symptoms, apathy and anxiety. Delirium is more frequent after haemorrhagic stroke, in older patients, and in those with medical complications. Denial is associated with hemispheric and basofrontal lesions and with neglect. It is more frequent in young and low education patients. A euthymic state seems necessary for the expression of denial. Catastrophic reaction is present in about 1/3 of acute stroke patients. Its relationship with non fluent aphasia or specific lesions sites is controversial. Hallucinations and other perceptual disturbances are uncommon out of the context of alcohol or drug withdrawal or epilepsy, but may follow occipital strokes. Reduplicative delusions for places or faces can occur in right hemispheric strokes and are examples of dissociation between perceptual recognition and the experience of familiarity. Strokes causing apathy include uni- or bilateral anterior cerebral artery infarcts, caudate, anterior or mesial thalamic and bilateral pallidal lesions. Apathy is associated with older age, executive cognitive impairment and major depression. Neurobehavioural syndromes in acute stroke may pose special difficulties to nursing and medical staff. Formal teaching on the neuropsychiatry of stroke should be included in the educational program of stroke units.

FW14–2

Acute aphasic syndromes

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Language disorders are a frequent occurrence in the acute phase of stroke. A brief evaluation of language function plays an important role in clinical assessment at this stage. The main goals of the assessment at this stage is the differential diagnosis with other neuropsychological impairments which may mimic or obscure the language disorders, as well as the collection of quantitative data which can be useful to monitor the evolution of cortical hypoperfusion. Most of the standardized aphasia test have been developed with different aims (aphasia classification and rehabilitation), and require an excessive time of administration to be useful for this purpose. A brief evaluation scheme must include a rating of oral expression, as well as quantitative measures of naming and auditory comprehension.

The pathophysiology of aphasia in acute stroke has been the focus of intensive investigation. The results of imaging studies of cerebral perfusion, using SPECT, PET, and, more recently; diffusion-perfusion MR imaging have indicated that the severity of the clinical picture in the acute stage reflects not only structural brain damage, but also potentially reversible hypoperfusion as well as "functional" distance effects (diaschisis). These findings have implications for studies of recovery and of treatment of acute stroke.

FW14–3

Unilateral neglect

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Unilateral hemineglect is characterised by lack or decrease of attention to stimuli and events in one hemispace, mostly the left, following contralateral lesion. In extreme cases, patients fail to react when spoken to from their left side, to eat food on left half of their plate, to shave or make up left half of their face or to read left side of a text. Hemineglect can affect to a varying degree visual, auditory, somatosensory and motor modalities. Formal tests include cancelling of items, copying or drawing of objects, dichotic listening or simultaneous tactile stimulation.

Anatomoclinical correlations stress the critical role of right hemispheric lesions in left unilateral neglect, including inferior parietal lobule, frontal lobe, thalamus, basal ganglia and internal capsula. Most cases, however, that are referred for clinical evaluation or for research projects on neglect may have bilateral lesions, as suggested by a recent study. Current models explain the laterality bias in neglect by postulating i) attentional gradients within each hemispace with differential roles for each hemisphere; ii) multimodal representations sustained by parieto-prefrontal networks; and iii) role of spontaneous eye movements in orienting attention.

The presence of hemineglect beyond the acute stage is associated with poor outcome. Rehabilitation strategies include left orienting, increase of attentional load on the left side, and readjustment of multisensory representations. Dopamine agonists were reported to improve neglect symptoms in some cases, but to worsen them in others.

In conclusion, unilateral neglect needs to be diagnosed and appropriate rehabilitation planned in the acute stage.

FW14–4

Apraxia

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Apraxia is defined as a "higher level" disorder of motor control. With the exception of so-called "limb-kinetic" apraxia, it differs from more "elementary" motor disorders by its distribution. Unilateral hemisphere lesion causes apraxia of both sides of the body. Apraxia is diagnosed by defective motor execution of three kinds of actions: Imitation of gestures, performance of meaningful gestures on command, and use of tools and objects. Apraxia is a sequel of left hemisphere damage and hence frequently associated with aphasia.

For acute stroke patients the ecologically most important domain of action affected by apraxia is use of tools and objects for activities of daily living (ADL). The impact of apraxia on independence in basic ADL is particularly important for patients with right-sided hemiplegia who are no longer able to perform ADL in routine ways and hence have to explicitly plan and control their performance. Both basic and more complex ADL can be improved by occupational therapy, but the success of therapy remains specific to the trained activities and does not generalize to non-trained ADL.

FW14–5

Alien hand syndrome

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Introduction Alien hand syndrome is a rare but important entity because of its enormous impact on everyday life of such patients.

Patients, methods and results Seven cases have been seen within 10 years, all were of vascular origin. The hallmark of this syndrome is the intermanual conflict, which refers to a collision of intentions seen or felt during motor actions. In a restricted sense it denotes a distinct type of behaviour containing motor elements that are directed against the willed action that is planned or about to be executed. We call this type of motor behaviour "Gegenarbeiten" in analogy to "Gegenhalten" in frontal lobe disease. Detailed investigations show that not only "Gegenarbeiten" occurs in such cases but a varying spectrum of motor disturbances which range from forced chronic grasping and groping to utilisation behaviour as well as apraxia and tactile anomia. If autocriticism is present there is always a sense of annoyance, astonishment or even panic visible and avoidance behaviour can result, though it rarely is effective to control "Gegenarbeiten" or grasping. Avoidance behaviour includes sitting on the "alien" hand, leaning against it, hiding it underneath the table, keeping objects out of reach, etc. In such cases, not only the anterior corpus callosum shows vascular damage but also frontomedial structures to a varying extent. "Gegenarbeiten" has not been seen in cases with isolated infarcts limited to the corpus callosum, agenesis or degeneration of the anterior corpus callosum, lipoma or glioma of the corpus callosum.

Conclusion It is held that "Gegenarbeiten" consists of elements of motor behaviour that is directed against the willed action. These elements of motor behaviour are a part of the normal motor executive process and are also generated under physiological conditions but usually are inhibited and therefore not visibly effective. They only become visible and deranging in their isolated form as they become disconnected from their inhibitory control areas due to damage to these frontomedial control areas and to the anterior corpus callosum

New advances in the understanding of nitric oxide (NO) mechanisms of migraine

FW15–1

New advances in the understanding of nitric oxide (NO) mechanisms of migraine

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Glyceryl-trinitrate (GTN) has been known to induce headache for almost a century but systematic studies of this headache were only undertaken in recent years. GTN induces a dose dependent headache in normal volunteers with a ceiling effect at 0.5 μg/kg/min. Migraineurs develop a more intense headache during a continuos GTN infusion than non-migraine volunteers and more importantly, migraineurs develop a delayed headache at an average latency of 5–6 hours after initiation of GTN infu-

sion. This delayed headache has all the characteristics of migraine without aura and in the patients' opinion it is exactly like spontaneous migraine attacks. The attacks are always without aura, also in patients whose spontaneous attacks invariably are with aura. It seems relatively independent of normal attack frequency and thus seems to be more related to the trait of migraine than to the state of migraine. GTN induced migraine attacks may be suppressed by pre-treatment with prednisolone and hence may depend on iNOS induction.
A similar immediate and delayed headache develops after histamine infusion and after calcitonin gen-related peptide (CGRP). While histamine probably works by stimulating endogenous production of NO, the mechanism of action of cGRP is unclear. GTN induced headache in volunteers and GTN induced migraine attacks in migraineurs both respond to sumatriptan.
Spontaneous migraine attacks can be treated effectively with an inhibitor of nitric oxide synthases, the enzymes catalysing the production of NO from L-arginine. Thus, NO is not only important in initiating the migraine attack but seems to be continuously involved in propagating pain mechanisms throughout the attack. Furthermore, using similar provocation and treatment principles it has recently been shown that NO is important also in chronic tension-type headache and in cluster headache.
In conclusion, if any molecule is "the headache stuff" then it is likely to be NO. Further exploration of NO related mechanisms of primary headache seems to be one of the most important research fields in headache today.

FW15–2

Induction of NOS Type II (iNOS) and inflammatory mediators in rat dura mater

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Nitric oxide (NO) has been implicated in migraine pathogenesis based on the delayed development of typical migraine headache 4–6 h after infusing the NO donor nitroglycerin [glyceryl trinitrate (GTN)] to migraineurs. Furthermore, inhibiting the synthesis of NO by treatment with a NO synthase (NOS) inhibitor attenuates spontaneous migraine headaches in 67% of subjects. Because NO has been linked to inflammation and cytokine expression, we investigated the delayed consequences of brief GTN infusion (30 min) on the development of meningeal inflammation in a rat model using doses relevant to the human model. GTN infusion caused dose-dependent Type II NOS [inducible NOS (iNOS)] mRNA upregulation in dura mater beginning at 2 h and an increase in the corresponding protein expression (mainly within resident meningeal macrophages) at 4, 6 and 10 h after infusion. Increased NOS Type II expression led to enhanced NO production within meninges, which could be attenuated by a selective iNOS inhibitor (L-NIL). iNOS expression is preceded by significant nuclear factor kappa B (NF-kappaB) activity, as reflected by a reduction in the inhibitory protein-kappa-Balpha (IkappaBalpha) and activation of NF-κB after GTN infusion. Iκ Bα degradation, NF-κB activation, and iNOS expression were attenuated by parthenolide (3mg/kg), the active constituent of feverfew, an anti-inflammatory drug used for migraine treatment. GTN infusion also caused a series of other events linked to tissue inflammation such delayed interleukin-6 release in CSF, delayed mast cell degranulation and NOS Type II dependent plasma protein leakage within dura mater.
These findings indicate that GTN promotes a delayed inflammatory response in dura mater and may offer an explanation for the development of migraine attacks in susceptible individuals.

FW15–3

Cyclic guanosine monophosphate (cGMP) and other second messenger mechanisms

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Nitric oxide (NO) donors induce dilatation of cerebral and extra-cranial arteries and migraine. The main effect of NO is to activate intracellular soluble guanylate cyclase and thus catalyze the formation of cyclic guanosine monophosphate (cGMP). Another possibly important molecule in migraine is calcitonin gene related peptide (CGRP), which activates production of cyclic adenosine monophosphate (cAMP). Levels of cAMP and cGMP are regulated by degradation as well as production. The cyclic nucleotides are degraded by the intracellular enzymes phosphodiesterases (PDE) of which 11 subtypes have been described in human tissues. The PDE's show different tissue, cellular and species distribution which makes then excellent targets for studying the effects of cyclic nucleotides in specific physiological systems such as the cerebral circulation and headache. In cerebral arteries of various animals the Calcium^{2+}/calmodulin-stimulated PDE1, the cGMP inhibited PDE3, the cAMP specific PDE4 and the cGMP specific PDE5 have been described, however the distribution on human cerebral tissue is not fully elucidated.
Recent studies show induction of headache and migraine when inhibiting the degradation of cGMP and this without dilatation of cerebral arteries. Whether this effect is also seen when inhibiting cAMP degradation is being investigated.
Phosphodiesterases may represent a possible cross talk and a feedback mechanism between the cAMP and cGMP signalling system, since cGMP may inhibit cAMP degradation and visa versa.
Furthermore, cGMP and cAMP have other targets in the cell; cyclic nucleotide dependent proteinkinases and ion-channels and these targets may represent a common pathway for the effects of cAMP and cGMP involved in migraine pathophysiology.

The role of ancillary investigations in the diagnosis of idiopathic normal pressure hydrocephalus (INPH)

FW16–1

The diagnostic problem of idiopathic normal pressure hydrocephalus (INPH)

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Idiopathic normal pressure hydrocephalus (INPH) is an important and common reason for gait disturbance and dementia in the elderly. The incidence is approximately 1 per 100.000 inhabitants per year. Treatment by ventriculo-peritoneal shunt implantation is successful in 30–80% of patients and the shunt complication rate is 15–50%. Selection of patients for surgery

is therefore of outmost importance and efforts of improving the success rate encouraged.
Instruments for predicting the effect of shunt surgery are clinical evaluation, morphological (brain CT or MRI) and functional examinations (cerebral blood flow) and cerebrospinal fluid (CSF) related examinations as pressure and frequency of B-waves registration, resistance and elastance measurements, distribution pattern (radionuclide cisternography), Biochemical and draining (CSF-Tap Test).
The workshop is dedicated to the presentation and discussion of these examinations with focus on three modalities, one established (CSF dynamic tests) and two newer (rCBF and CSF biochemical analysis) used for selection of patients for surgery. The discussion will focus on the predictive value of these methods in relation to other established methods as MRI.

FW16–2

ICP registration and CSF infusion studies

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Introduction Cerebrospinal fluid (CSF) dynamic evaluation is generally accepted as an important supplementary investigation in the selection of shunt responsive patients with idiopathic normal pressure-hydrocephalus (INPH). However, the prognostic value of lumbar measurement of the resistance to CSF outflow (R_{out}), versus intraventricular ICP monitoring with the assessment of B-wave activity, is strongly debated. The results of restricting the evaluation from an intraventricular assessment to a lumbar infusion test (LIT) are presented.
Methods All patients >18 years of age referred with clinicoradiological suspicion of INPH (n=33) were subjected to a LIT. Subsequently a combination of strict criteria concerning the results of the LIT and the clinical presentation determined whether to proceed with (a) further intraventricular CSF dynamic evaluation, (b) shunt surgery or (c) no further diagnostic or operative engagement.
Results According to the algorithm of the study program, the decision on shunt surgery was settled in 80 percent of the patients after *exclusively* a LIT, of whom 82 percent improved after shunt insertion. In the small subgroup of patients representing cases of doubt after the LIT, no supplementary valuable information was gained by performing an additional intraventricular CSF dynamic evaluation. Accordingly, the overall shunt success rate was 76 percent.
Conclusions In cases evaluated for NPH, the LIT is equally effective, compared to an intraventricular assessment, in settling whether shunt operation is indicated or not. The practical and economical consequences are substantial – the LIT may be performed in an outpatient setting with no need of hospitalisation and neurointensive care.

FW16-3

The role of cerebral blood flow (CBF) and cerebrovascular reserve capacity in the diagnosis of idiopathic normal pressure hydrocephalus (INPH)

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Introduction Quantitative PET-studies were set out to clarify the role of CBF measurement in diagnosing INPH.
Methods In patients selected for surgery $^{15}0$-H_20-PET was performed before, one week (7d) and 7 months (7m) after treatment. In 70 patients global CBF (ml/100ml/min) was measured and in 45 patients also the cerebrovascular reserve capacity after 1g acetazolamide application (CVR; %). Regional differences (rCBF) in [^{15}O]H_2O-uptake were analysed using Statistical parametric mapping (SPM99) software (Z>3.09). Clinical outcome was assessed after 7 months using the RANKIN-score (responders n=39; non responders n=31).
Results Before surgery, CBF was impaired in patients compared to controls: 36.5±0.5 vs. 48.3±5.9($p<0.001$). CBF in clinical responders was significantly lower compared to non-responders: 35.0±7.6 vs. 40.0±13.5 (p=0.03). The accurate predictive value of distinct clinical parameter, taken CBF in addition, increased from 0.76 to 0.89. CVR was varying and impaired (<30%) in one third of patients (15/45). After shunting, CVR increased in responders: 37.1±12.5 (pre), 54.1±38.4 (7d) and 55.8±32.75 (7m); p=0.04. In non-responders CVR decreased at one week: 41.6±25.7 (pre) and 32.6±22.2 (7d), n.s. Thus, early changes in CVR at one week correlated with clinical outcome (p=0.006, logistic-likelihood-ratio-test). The degree of clinical impairment before surgery correlated with reduced activity in an extended area (1239voxel) in the mesiofrontal cortex (Z=4.41, p=0.002) and the anterior temporal cortex (Z=4.07, p=0.002). After shunting, frontal activity increased in responders (241voxel, Z=4.47, p=0.007), while non-responders displayed corresponding CBF decreases (955voxel, Z=4.35, $p<0.001$).
Conclusions Taken in combination with "traditional" methods, CBF and CVR measurements may improve predictive accuracy in equivocal cases. Also, regional CBF has underlined the significance of supplementary motor areas for psychomotor retardation in INPH.

FW16–4

White matter changes and CSF biochemical analysis

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White matter changes in the periventricular region is a hallmark of idiopathic normal pressure hydrocephalus (INPH). In spite of a primarily different pathogenesis patients with Binswanger disease (BD), probably the most important differential diagnosis, can present with similar symptoms and exhibit white matter changes that are difficult to distinguish from those of INPH constituting a major diagnostic and therapeutic challenge.
We analysed CSF markers reflecting demyelination and axonal degeneration in patients with INPH and BD in order to evaluate the diagnostic, predictive and pathophysiological significance of white matter pathology in these disorders.
Sulfatide, a marker of demyelination was increased in all BD patients distinguishing between BD and INPH patients with a sensitivity of 74% and a specificity of 94% making it a potential diagnostic marker. Normal sulfatide levels in most INPH patients suggest minor or no demyelination in NPH. High CSF levels of neurofilament protein (NFL), a marker of neuronal degeneration, correlated with severity of symptoms and with a favourable outcome after shunt surgery, which suggests that the symptoms in NPH are, related to periventricular white matter changes. CSF sulfatide correlated with the segmented amount of MRI deep white matter hyperintensities (DWMH) and NFL

with both periventricular hyperintensities (PVH) and DWMH suggesting that DWMH might relate to demyelination and PVH to neuronal axonal dysfunction.
CSF sulfatide could be a potential diagnostic marker in INPH and BD. Increased CSF NFL may be a marker of ongoing but still reversible axonal dysfunction in INPH. The diagnostic and predictive value of these markers is being investigated in a prospective study.

Hyperbaric oxygenation (HBO): a new therapeutic method in neurology

FW17–1

What is hyperbaric oxygenation? How is it administered, dose.

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Introduction Hyperbaric oxygenation therapy (HBOT) is the use of 100% oxygen at greater than atmospheric pressure. It adheres to all of the gas laws of physics. Edward Teller, father of the hydrogen bomb, stated that, with hyperbaric oxygenation, free molecular oxygen is delivered directly to the cell for immediate metabolic use without energy exchange, even with compromised circulation. No drug or combination of drugs could ever match these physiological properties.
Methods Administration may be either in a single monoplace chamber compressed with 100% oxygen or in a large chamber holding between 2 and 30 patients, where the compression takes place with air and oxygen delivered by mask or hood. There are specific doses for various problems, similar to insulin for the diabetic.
Results On a worldwide basis, the primary uses of hyperbaric oxygen are for decompression illness, carbon monoxide intoxication, and wound healing. Newer advances in the field indicate that it may play a significant role in the field of neurology because of the delivery of oxygen directly to the cells. This would be both in acute neurologic insults and in long-term neurorehabilitation.
Conclusions Hyperbaric oxygenation, a well-known treatment for select indications, is now expanding into the field of neurology for both the acute and the long-term cases. Further studies are required, and this may hold significant possibilities as a new modality for the neurologist in early intervention and long-term neurorehabilitation.

FW17–2

Effects of hyperbaric oxygenation on the central nervous system

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Introduction Hyperbaric oxygenation has significant effects in acute brain insults. It reduces cerebral edema, intracranial pressure, lactate toxic amine levels, and limits the ischemic cascade. Its use in acute ischemic thrombotic stroke is being evaluated. In acute brain insults and late neurorehabilitation, it reactivates the ischemic penumbra up to 12 years and enhances plasticity.
Methods Hyperbaric oxygenation has a specific dose for acute and long-term neurologic problems. Over 500 patients with brain injuries including stroke, traumatic injuries, and anoxic toxic encephalopathies, have been treated at the Ocean Hyperbaric Neurologic Center. In most cases, single photon emission computerized tomography (SPECT) scanning was utilized as a baseline and followed sequentially. Treatments ranged from 20 to 600 hours, at pressure of 1.1 in seizure disorder and 1.75 ATA. All patients were videotaped.
Results In acute brain insults, results are dramatic. In late cases, dormant, idling neurons may be reactivated and fire electrically for up to 12 years after ictus. PT, OT, speech, acupuncture, nutritional counseling, and herbal supplements encompass part of the program. There is a high correlation between the positive changes in the SPECT scans and the clinical changes in the patient. SPECT scanning in long-term stroke, traumatic brain injury, and anoxic ischemic encephalopathy will be presented.
Conclusions Hyperbaric oxygenation may play a major role in acute and long-term rehabilitation. An evolving role is feasible. Reductions in morbidity and mortality, as well as cost effectiveness, are major considerations.

FW17–3

Oxygen deficiency of the brain and hyperbaric oxygenation – in vitro and in vivo studies

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Background Hypoxia critically influences secondary brain lesions after stroke or injury, as is revealed by neuromonitoring in brain injured patients.
Increased tissue supply of oxygen using high pressure is the rationale behind hyperbaric oxygenation (HBO). Experimental and clinical data indicate a HBO benefit with traumatic or ischemic brain lesions.
Material and Methods Ischemia was simulated in rat brain slices in vitro. Anoxic depolarization (indicator of ischemic stress), evoked potentials (EP, a measure of functional integrity), and amino acid release measured by in vitro microdialysis were correlated.
Cerebral ischemia was induced for 30min using the Pulsinelli model in rats. Survival time and electrical brain activity of HBO treated animals were compared with controls.
HBO (≤1.5 ATA, 45min, 15 repetitions) was applied in every second of 99 patients with traumatic mid-brain syndrome.
Results With early reoxygenation of brain slices, EP recover partially without the release of excitotoxic transmitters, even though depolarization occurs. Longer ischemic periods lead to complete EP extinction.
Survival rate of Pulsinelli rats under HBO was eightfold higher compared to controls.
Survival time and survival rate of brain injured patients were better under HBO: 53% (HBO) vs. 74% of patients died or remained apallic. 33% (HBO) vs. 6% of patients completely recovered.
Conclusion In severe "energy crisis" of the brain HBO may prevent secondary damage. A randomized study in patients with severe brain lesions and bad prognosis revealed a distinct benefit from HBO especially in younger patients. Further investigations on HBO effects are promising.

FW17–4

Neurologic decompression sickness – the diagnosis and short term result of treatment

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The diagnosis of neurologic decompression sickness (DCS) in divers is based on the onset of neurological symptoms within the first hours after a dive. According to previous studies the most common site for the neurological lesions is the spinal cord. In this study we wanted to evaluate the neurological symptoms of divers with DCS to determine the location of the lesion or lesions, and the effect of hyperbaric oxygen (HBO) treatment.
Method In Norway most divers with possible neurologic DCS are examined and treated at the University Hospital of Haukeland and the Royal Norwegian Navy, Haakonsvern Naval Base. All divers treated during the period 1999–2001 are included in this study.
Results A total of 54 divers were included, 45 men and 9 women. The neurologic symptoms were headache, fatigue, unconsciousness, vertigo, paresis, sensibility changes, pain and imbalance. Forty-seven were classified as having mainly cerebral involvement and 6 spinal involvement. After HBO treatments 31 still had some symptoms. Four of the 6 divers with spinal DCS had persisting significant paraparesis.
Conclusion Cerebral involvement was more common in this population compared to previous clinical series of patients with neurological DCS. The HBO treatment was most effective in the group of divers with cerebral DCS.

FW17–5

Oxygen baths in patients with discirculatory encephalopathy

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Aims To evaluate the effect of oxygen baths (OB) in the patients with discirculatory encephalopathy.
Methods 99 patients subdivided into two randomized groups were evaluated. Group I received OB, group II received fresh water baths ("placebo"). Oxygen partial tension had been evaluated using transcutaneous method. Coagulation and anticoagulation mechanisms, blood rheologic properties had been measured as well.
Results At the initial state the patients developed the reduction of pO2 levels in skin, the restriction of the functional reserves of microcirculatory flow, the increase of aggregation activity of thrombocytes, the functional activity of Willebrand factor and concentration of fibrinogen and also the increase of viscosity, aggregation activity of erythrocytes, the reduction of their deformity. OB, especially a 3–4.2 mmol/l concentration as different from that of "placebo" has a significant effect on clinical course of a disease, hemostatic system of blood rheology. They cause the increase of pO2 and skin oxygen consumption, the improvement of the state of microcirculatory flow. These alterations are concomitant with the reduction of aggregation activity of thrombocytes, concentration of fibrinogen, Willebrand factor and activation of fibrinogen that indicate to the reduction of thrombogenic potential of hemostasis. The reduction of hematocrite levels, viscosity and aggregation activity of erythrocytes as well as the increase of their deformity is the evidence of the improvement of blood rheologic properties after OB.
Conclusion OB is an effective method of balneotherapy in the patients with discirculatory encephalopathy.

FW17–6

Hyperbaric oxygen therapy (HBO_2) in the treatment of ischemic anoxic encephalopathies

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Background Conventional treatment has not been able to significantly modify the morbidity/mortality of ischemic anoxic encephalopathy (IAE). HBO_2 has proven to be effective in reducing the primary and secondary phases of ischemia/reperfusion injury in several areas of the body and could make the difference in the acute management of IAE.
Purpose Literature revision of articles published in MEDLINE to determine the value of HBO_2 in the treatment of acute IAE.
Materials and Methods Patients treated acutely with hyperbaric oxygen for IAE. Statistical analysis of results of controlled and uncontrolled studies with patients treated with HBO_2.
Results When HBO_2 is administered early, it has proven to modify statistically the tissue levels of ATP, avoid the conversion of xanthine dehydrogenase to xanthine oxidase, avoid the production of reactive oxygen species, reduce the expression of adhesion molecules (ICAM-1, Integrin β_2), reduce the production of interleukines (1, 6, 8, TNFα and PAF), normalize several lab studies (hemoglobin, hematocrit, total proteins, sodium, triglicerides, direct billirubin, pH), and reduce the morbidity and mortality.
Conclusions When HBO_2 is administered early, it is a safe and effective treatment in reducing the damage of ischemia/reperfusion injury responsible of the early pathogenesis of acute IAE. A prospective, randomized, controlled and double-blinded study is needed to determine the real use of HBO_2 in acute IAE.

FW17–7

Emergency life saving use of high doses of oxygen in neonates

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Background The morbidity/mortality of neonatal severe hypoxia has not been modified in the last 30 years. High doses of oxygen has proven to be effective in reducing ischemia/reperfusion injury and when used acutely in neonates it is life saving and reduces the long lasting neurological disabilities.
Purpose Prospective progressive pilot study performed in neonates with severe hypoxia to determine the value of high doses of oxygen used acutely.
Materials and Methods Patients (n=5) treated acutely with high doses of oxygen for severe hypoxia. Laboratory exams, transfontanelar ultrasound, EEG, X-rays and funduscopic studies were performed before and after the 45-minute treatment.
Results When administered early, high doses of oxygen proved to statistically significant modify hemoglobin, hematocrit, total proteins, serum sodium, triglicerides, direct bilirubin and pH. Dramatic improvement was observed in EEG, transfontanelar ultrasound and x-rays within 12 hours of the treatment. All the funduscopic exams were negative. One patient developed pulmonary oxygen toxicity. A two-year follow-up showed no mortality related to treatment and adequate neurological development.

Conclusions When administered properly, appropriately and early, a single 45-minute treatment of high doses of oxygen, modifies the lifespan and dramatically reduces the morbidity of neonates with severe hypoxia. Although a controlled study is needed, we believe that this treatment should be available in every hospital for the management of neonates with severe hypoxia.

FW17–8

Hyperbaric oxygen therapy for children with cerebral palsy: A multicenter placebo controlled randomised clinical trial

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Background Based on numerous anecdotal reports and on results of pilot studies, it has been claimed that hyperbaric oxygen therapy (HBO) is a valuable treatment of children with cerebral palsy (CP). However, there is no scientific evidence of the efficacy of HBO in this condition. We have conducted a randomised trial to assess the efficacy and side effects of HBO therapy in children with CP.
Material and Methods 111 children with CP aged 3 to 12 years were randomly allocated to HBO (n=57) or slightly pressurised room air (n=54). All children received 40 treatments over a 2-month period. HBO treatment consisted in one hour exposure to 100% O_2 at 1.75 atmospheres absolute (ATA) while patients on slightly pressurised air received air at 1.3 ATA. The main outcome measure was gross motor function. Secondary outcomes included performances in daily living, attention, working memory and speech.
Results For all outcomes, both groups improved significantly over the course of the study but without any difference between the 2 treatment arms. The Gross Motor Function Measure (GMFM) score increased by 3% on average in the children on slightly pressurised air and 2.9% in those on hyperbaric oxygen: mean difference between groups = –0.40 95% CI (–1.69; +0.90); p=0.544. Other important changes were observed for speech, memory and functional skills. Ear problems were observed in 27 children treated by HBO and 15 treated by placebo (p=0.004).
Conclusion The study demonstrated that children in both groups improved substantially with respect to gross motor function which was the main outcome but also with respect to speech, attention, memory and functional skills, which were the secondary outcomes. However, improvements measured in children who received hyperbaric oxygen were not greater than those observed in children who received slightly pressurised air. In our opinion, there are two main hypotheses to explain these results. The improvements seen in these children could result from the mere act of participating in the trial. This participation effect could be due the fact that the parents were highly motivated and that the context of the intervention was a source of positive communication with other children and parents. The other hypothesis is that both treatments were equally effective and that low pressure hyperbaric therapy could produce a global improvement in children with cerebral palsy. There are no definite scientific evidences that could validate either one of these two hypotheses. However, several clinical or experimental observations could support both explanations and these will be critically reviewed. It is clear that further research is needed in order to define the role of hyperbaric therapy in chronic neurological diseases.

Laboratory evaluation of autonomic function in neurological practice

FW18–1

Standards for diagnosis of neurogenic orthostatic hypotension and syncope

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Syncope is defined as a temporary interruption of cerebral perfusion with a sudden and transient loss of consciousness and spontaneous recovery. Weakness, headache, blurred vision, diaphoresis, nausea, and vomiting may occur during presyncope, i.e. prior to loss of consciousness. Among cardiovascular causes are arrhythmia, structural and coronary heart disease. Neurological, metabolic, and psychiatric and other unexplained etiologies account for non-cardiovascular etiologies.
Orthostatic hypotension – a frequent cause of syncope – has manifold etiologies comprising neurological and internal diseases. Orthostatic hypotension usually results from impaired peripheral vasoconstriction or reduction of the intravascular volume. Usually, blood pressure decreases and induces the above prodromi shortly after standing up. Frequently, autonomic cardiovascular modulation is reduced.
Many patients with "unexplained" syncope experience neurally mediated or neuro-(cardio-)genic syncope. Neurogenic syncope can be associated with pain, stressful situations, anxiety or fear, prolonged standing or specific triggers such as micturition, defecation, coughing or sneezing, visceral or carotid sinus stimulation, trigeminal or glossopharyngeal neuralgia. In contrast to orthostatic hypotension due to autonomic failure, cardiovascular control may be stable for an extended period of time during orthostatic stress, then blood pressure and heart rate decrease suddenly.
Examination of syncope patients should include a detailed history, internal and neurological examination, standard laboratory evaluation, electrocardiogram and a Schellong test, i.e. blood pressure and heart rate monitoring at rest and during at least ten minutes standing.
Additional cardiological and neurophysiological procedures, metabolic screening including an oral glucose tolerance test, and a psychiatric evaluation can identify specific etiologies.
Hypotension occurring within the first (3–5) minutes after orthostatic challenge requires autonomic testing with assessment of heart rate variability and preferably also blood pressure modulation, baroreflex sensitivity, sudomotor function and catecholamine levels.
Neurocardiogenic syncope requires prolonged orthostatic challenge, e.g. by passive 60° to 70° head-up tilt testing. The sensitivity of this test can be improved by additional pharmacological provocation, e.g. by isoproterenol, or by increased orthostatic stress using lower body negative pressure stimulation, or by emotional stimuli, a Valsalva maneuver and massage of the carotid sinus.

FW18–2

Standards for the evaluation of heart rate variability

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The use of Heart Rate Variability (HRV) in a clinical setting has gained a wide popularity not only because of its prognostic power in a series of cardiovascular conditions (post myocardial infarction, congestive heart failure, arrhythmias) but also because spectral analysis can provide sensitive markers of autonomic regulation of the SA node. Disturbances of autonomic regulation have usually been addressed by a combination of clinical tests, requiring the active collaboration of patients, or based on invasive procedures (NorEpinephrine spill-over, sympathetic microneurography). As with any methodology, the crucial need for standards of execution and interpretation was eventually addressed by a consensus document (Circulation 1996), focusing mostly on cardiovascular applications. Autonomic regulation is best inferred considering not only mathematical and modeling aspects, but also (if not especially) physiological underlying mechanisms, with dynamic protocols. These latter ones are particularly important in the case of neurological and behavioral applications. In the presentation we will focus on the various components of the clinical applications of HRV, considering in particular: physiological background, mathematical models, clinical inference, based on a multiparametric approach, viewed in a progressively more3 complex design. Standardization of study protocols will also be addressed. The general model is that data from the physiological domain, i.e. oscillations in HRV, at a low (LF) and high (HF) frequency, because of their strong coherence with similar LF and HF oscillations in the activity of peripheral or central neural structures involved in autonomic regulation, can, in the information domain, provide a means to predict normal and abnormal behavior of the autonomic nervous system.

FW18–3

Minimal technical standards for an autonomic lab: a European survey

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Introduction Investigations of the autonomic nervous system (ANS) is performed by specialised research laboratories, routine electrophysiological labs, neurologists and non-neurologists. New and sophisticated diagnostic technologies are introduced and become also increasingly commercially available. Minimal standards for clinical routine diagnostics in ANS labs become desirable. Yet, we even do not know the number of ANS labs existing in Europe and the methods used by them.

Objectives Data shall be collected on the number of ANS labs in Europe and their distribution in the individual countries. Further, methods and equipments used in different labs shall be evaluated.

Methods A questionnaire has been developed and was distributed to neurological and non-neurological labs involved in ANS investigation either directly by us or by the local representative of the EFNS panel for ANS in Western and Eastern Europe.

Results There is a heterogeneous distribution of labs throughout Europe. Cardiovascular and sudomotor testing are the most frequent investigations. Concerning the equipment no standards seem to exist but a wide variability with many self-made devices. However, many investigators implement normative data from the literature.

Conclusion We found considerable amount of variability concerning distribution and equipment throughout Europe. Our data show that minimal standards for routine ANS testing have to be established in order to compare results of diagnostic evaluations. Standards may also help to equip new labs, evaluate existing ones and test commercially devices.

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