



GfB
Gesellschaft
für Biofaktoren



FOUNDATION OF THE
SOCIETY FOR THE STUDY OF
NEUROPROTECTION AND
NEUROPLASTICITY

The Society for Biofactors

under the umbrella of the

Foundation of the Society for the Study of
Neuroprotection and Neuroplasticity

is organizing the

SYMPOSIUM

BIOFACTORS IN METABOLIC DISEASES



8th September 2016, 17:00 - 19:00
Ramada Parc Hotel
Terra Hall
Bucharest, Romania



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THE SOCIETY FOR BIOFACTORS

It was founded as an independent, non-profit organisation in 1994.

Its aim is to provide information about the underlying science and the possibilities of using biofactors in order to stabilise health as well as prevent or treat illnesses. It provides articles and recommendations, for example, about:

- healthy diet
- prevention of diet-related diseases
- mode of action of individual biofactors and the consequences of a deficiency
- promotion of further and advanced training for health professionals
- support for science and research

With its activities, the society addresses not only professionals, but also laypersons. It evaluates research results, draws up informed opinions on current topics from the field of biofactors, organises and comments on symposia and congresses.

The Society for Biofactors exchanges information and experience with specialist groups. Here, it works together with doctors, pharmacists, nutritionists, clinics, universities, associations, alternative practitioners, healthcare providers, self-help groups, publishers and the pharmaceutical industry.

www.gf-biofaktoren.de

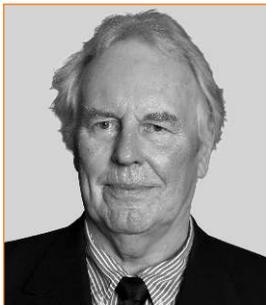


FOUNDATION OF THE SOCIETY FOR THE STUDY OF NEUROPROTECTION AND NEUROPLASTICITY

The Foundation of the Society for the Study of Neuroprotection and Neuroplasticity is a scientific organisation focusing on creating discussions forums at the highest scientific level for future research so as to discover new ways that work for the benefit of neurotrophicity, neuroprotection and neuroplasticity. We are creating bridges between the academic environment, practitioners and researchers by setting up international advisory groups. To outline the future, to state truly and accomplish the goals of our foundation, an international congress is organized yearly - an open stage for debates and updated theories in the field.

The Foundation gets involved in ongoing educational processes for young specialists, like the International School of Neurology, the European Teaching Course on Neurorehabilitation and basic and clinical research projects in the field.

For more information, please visit our website:
www.ssn.ro



Hans-Georg CLASSEN

Prof. Dr. med.

Head of the Department of
Pharmacol and Toxicol of
Nutrition, University
Hohenheim

Editor of “Arzneimittel-
Forschung/Drug Research“

President of the Society for
Magnesium Research;
Honorary President

Chevalier des Palmes
Académiques

Dean of the Faculty: General
and Applied Sciences,
Hohenheim

One only sees what one knows!

Biofactors include vitamins, minerals, trace metals, amino acids, fatty acids and vitamin-like substances, i.e. physiological substances regulating metabolism.

Biofactors are necessary to avoid or compensate for overt or latent states of deficiency; at higher concentrations they may possess therapeutic and at excessive supply even toxic effects. According to most nutrition experts a varied and balanced food consumption also covers the supply of all biofactors; this however applies only to an otherwise healthy population. People on special diets, e.g. vegans, persons on diets to reduce their weight (note: “diet is to die with a t”), or pregnant women do need certain supplements. This is especially true for patients suffering of metabolic diseases and/or those treated with drugs affecting enteral absorption, metabolic availability or excretion of biofactors.

In view of the great interest in the scientific activities of the GfB in Germany, we decided to take part in the Bucharest International Symposium. The actual topic relates to diabetes and associated metabolic disturbances; for further topics you are invited to visit our WEBSITE, available also in an English version.

I thank all organizers, speakers and last but not least the audience for their support and wish you a stimulating session.

Prof. Dr. Hans-Georg Classen,
Chairman of the GfB



Tudor LUPESCU

M.D., Ph.D., Senior
Specialist in Neurology

Chair of Neurological
Department, “Prof. dr.
Agrippa Ionescu”
Emergency Clinical
Hospital, Bucharest,
Romania

Vice President of the
Society for Diabetic
Neuropathy

President of ASNER -
Society for
Electrodiagnostic
Neurophysiology of
Romania

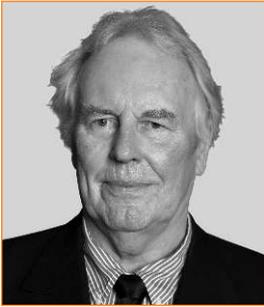
Dear Friends,
Dear Colleagues,

It is an honour for us to host the International Symposium for Biofactors in Romania this year. The Society for the Study of Neuroprotection and Neuroplasticity has always supported knowledge regarding any biological influence on the human nervous system. This is why we consider that this meeting will provide important information for the attendees. As medical practitioners mainly concerned with pathophysiological reasoning, clinical data, and different treatment options, we are quite often inclined to skip over basic, fundamental issues like the involvement of biofactors in normal, physiological functioning of the nervous system. Recent (and not only) data tend to underline the role of biofactors in some neurological conditions. We all know about the role of B vitamins in diabetic neuropathy. Thiamine deficiency is involved in the development of Wernicke encephalopathy. Vitamin D deficiency has been clearly correlated with multiple sclerosis. Long time treatment of diabetic patients with metformin has been shown to generate vitamin B12 deficiency. For me personally, being more concerned with neuromuscular diseases, I am aware of the prevalence of vitamin B12 deficiency as cause of sensory polyneuropathies and/or myelopathy, and of the possible toxic neuropathic effect of excessive administration of vitamin B6.

The program of this symposium is very interesting. Prof. Hans Georg Classen will shape the general outline of the involvement of biofactors in neurology. Prof. Joseph Borbola will talk to us about the role of magnesium orotate in diabetes, whereas Prof. Alin Știrban will speak about benfothiamine in the same disease. In the second part of the symposium Prof. Reiners will present the role of vitamin B12 in neurological disorders, and finally, my colleague, Prof. Gabriel Prada will share his experience regarding vitamins in metabolic diseases and geriatrics. I hope that this symposium will add value to our medical knowledge, and I kindly invite all my colleagues to participate in this symposium. Finally, allow me please to show my gratitude to the “Gesellschaft für Biofaktoren” for accepting the invitation to organize this International Symposium here, in Bucharest.



	Chairman: Prof. Dr. med. Hans-Georg Classen, Stuttgart, Germany Dr. Tudor Lupescu, Bucharest, Romania
16:30	WELCOME SNACK
17:00 - 17:10	Introduction <i>Biofactors in neurological and metabolic diseases</i> Prof. Dr. med. Hans-Georg Classen, Stuttgart, Germany
17:10 - 17:30	<i>The role of magnesium orotate in the therapy of cardiovascular diseases</i> Prof. Dr. Joseph Borbola, Budapest, Hungary
17:30 - 17:50	<i>Benfotiamine in the treatment of diabetic complications</i> Prof. Dr. Alin O. Știrban, Düsseldorf, Germany
17:50 - 18:05	COFFEE BREAK
18:05 - 18:25	<i>Vitamin B12 in neurological disorders</i> Prof. Dr. med. Karlheinz Reiners, Würzburg, Germany
18:25 - 18:45	<i>Vitamins in metabolic diseases and geriatrics</i> Prof. Dr. Gabriel-Ioan Prada, Bucharest, Romania
18:45 - 19:00	<i>Discussion</i>
19:00	EVENING EVENT



Hans-Georg CLASSEN

Prof. Dr. med.

Main Previous Positions:

- Head of the Department of Pharmacol and Toxicol of Nutrition, University Hohenheim
- Editor of “Arzneimittel-Forschung/Drug Research“
- President of the Society for Magnesium Research; Honorary President
- Chevalier des Palmes Académiques
- Dean of the Faculty: General and Applied Sciences, Hohenheim

Present Position:

Emeritus since 2001

Since 1994: Chairman of the Society for Biofactors

Publications, Research Topics:

More than 330 papers, >170 citable articles,
7 Handbook articles

Research Topics:

Electrolyte metabolism, Magnesium and stress, nitrate/nitrite, biofactors in health and disease

BIOFACTORS IN NEUROLOGICAL AND METABOLIC DISEASES

Liebig's *law of the minimum* tells that the capacity of a barrel with staves of unequal length is limited by the shortest stave, or, to put it more plainly, a chain is only as strong as its weakest link. In 1895 the minimum law was broadened by Liebscher's *optimum law* determining the level at which the conditions are the most favourable. These findings from agricultural sciences also apply to biofactors: their sufficient availability is necessary to avoid or compensate for deficiency states, and at higher concentrations, they may possess therapeutic effects as shown by the following examples:

Alcoholic Wernicke-Korsakoff encephalopathy is usually treated with thiamine (Vit B1) to increase transketolase activity responsible for the metabolism of glucose via the pentose-5-phosphate shunt. However transketolase requires not only thiamine pyrophosphate, but also Mg as a co-factor. Hence Mg-deficient alcoholics were unresponsive to vitamin B1 until their Mg was repleted (J. Neurol, Neurosurg, Psychiatry 1974; 37: 59-62; Scottish Med J 2013; 58: 139-42).

Mg deficiency is frequently associated with hypocalcemia despite an adequate intake of calcium and Vitamin D (Am J Clin Nutr 1964; 15:133-43), a syndrome called "*Ca-resistant hypocalcemic hypomagnesemia*". The underlying mechanisms are: decreased activity of Mg-dependent renal 1-alpha-hydroxylase converting 1, 25-(OH) Vit D to its active form 1,25-(OH)₂, and impaired secretion and impaired target responsiveness to parathormone. This helps to understand the effectiveness of Mg supplements in the treatment of the tetanic syndrome.

Ionic pumps (Na-K-ATPase; Ca-ATPase) which are necessary for the maintenance of intracellular electrolyte equilibrium are Mg-dependent. Hence, Mg deficiency is obligatorily associated with secondary electrolyte alterations, namely intracellular K-depletion despite adequate K-intake and Na- and Ca-overload. Thus Mg deficiency favours the development of arterial hypertension and generally of spasms.

Mg deficiency impedes pancreatic insulin secretion, and the insulin receptor (tyrosinkinase) needs Mg for activation. Hence the compensation of Mg deficiency improves glucose balance (Diabetologie 2014; 9: 96-100).

Finally, many pharmaceuticals are "robbers" of bioactors (e.g., B-vitamines, folic acid, Mg, Ca, K) and need adequate supplementation (see *www.gf-biofaktoren*; keyword: "vitamin robbers").



Joseph **BORBOLA**

PhD., FESC

Prof. Dr. Joseph Borbola was born in Holczminden (Germany) and received his MD from the Albert Szent-Györgyi Medical University of Szeged, Hungary in 1970. He completed several fellowships in Internal Medicine and Cardiology in Hungary, later at the Tübingen Medical University (Germany, 1975), Harvard Medical School (Prof. Dr. B. Lown's Cardiovascular Clinic) (1985-1986) in Boston, Rush-Presbyterian Medical University (1986-1987) in Chicago, later in Madrid (1992). He has been working at the Hungarian Institute of Cardiology, Budapest since 1975, first as the chief of Arrhythmia Service and Cardiac Electrophysiology /Ablation Division, and later as the Head of the Department of Adult Cardiology. He became Professor of Cardiology in 1998. His primary research interests include invasive and non-invasive diagnostics and treatment (including antiarrhythmic drugs, transcatheter ablation, pacemakers, ICDs) of cardiac arrhythmias. He has published important scientific data on basic and clinical cardiac electrophysiology, SAECG, ablation and ICDs.

Prof. Dr. Joseph Borbola became a fellow of the ESC in 1990. He had an European Diploma of Cardiology (2000). He served at the Board of the ESC, as councillor (1996-1998). He was awarded with a silver medal of the ESC (1998). He is a Honorary Member of San Marino Society of Cardiology. Currently, he is a Board Member of the World Society of Arrhythmias.

He served on several professional editorial board, and has been widely recognized for his work in the field of Cardiology. He is well published, having authored ten books, and had more than 320 scientific papers, published in national and international journals.

THE ROLE OF MAGNESIUM OROTATE IN THE THERAPY OF CARDIOVASCULAR DISEASES

Magnesium is an essential, mainly intracellular divalent cation, which plays a vital role in human biochemical processes acting as a coenzyme in different, more than 300 ATP dependent reactions including the production, stability and utilization of polyphosphate compounds. Magnesium has also a special role in the regulation of transmembrane ion transfers in cardiac cells. Some evidence suggests that high dietary magnesium intake plays a protective role not only in cardiovascular risk factors, but also in sudden cardiac (arrhythmic) death and in coronary artery disease. Recent findings from a large prospective study showed an inverse, significant association between dietary magnesium intake and cardiovascular, cancer and all-cause mortality in Mediterranean individuals at high risk of cardiovascular disease.

Magnesium orotate is a unique pharmaceutical preparation where the orotic ions are functioning not only as an intracellular magnesium carrier, but also as an important cofactor for uridine, DNS, RNS synthesis. It is used to treat magnesium deficiency and hypomagnesemia as well as cardiovascular diseases including hypertension, cardiac arrhythmias, coronary artery disease and chronic systolic heart failure.

Magnesium raises the atrial and ventricular electrical thresholds, decreases the sinus rate, prolongs the sinus node recovery time and the AV-nodal conduction time and refractoriness. These characteristic actions place magnesium in the group of physiologic calcium antagonists. Additionally, magnesium influences the occurrence of cardiac arrhythmias by altering early and late after potentials inducing triggered activities. Main antiarrhythmic indications for magnesium therapy are: torsades de pointes ventricular tachycardias, digitalis-induced ventricular tachyarrhythmias, multifocal atrial tachycardias and perioperative cardiac arrhythmias in heart-surgical patients. Additionally, magnesium has been used successfully as an additive therapy before electrical cardioversions and during IV. class III. antiarrhythmic drugs for enhancing their antiarrhythmic activity and for decreasing the potential proarrhythmic action in patients with atrial fibrillation or flutter. Oral magnesium orotate has been used for many years in patients with symptomatic premature atrial or ventricular contractions in stable coronary artery disease or in heart failure patients on diuretic therapy.

Magnesium orotate has been used as adjuvant therapy in patients on optimal, guideline recommended treatment for systolic heart failure, increasing survival rate and improving clinical symptoms and patient's quality of life. Magnesium orotate represents a unique, time-honoured magnesium therapy in cardiovascular medicine.



Ovidiu Alin ŞTIRBAN

Ph. Dr. med.

Head of the Diabetes and Endocrinology Department,
Sana Klinikum and Sana Arztpraxen, Remscheid, Germany

Heinrich-Heine University Düsseldorf: lecturer

President of the German-Romanian Association for the Study of
Diabetes Complications.

Founding member of the Romanian Society for Diabetic
Neuropathy

Board member of the Neuropathy Working Group of the
German Diabetes Association (DDG)

Co-Editor-in-Chief of the “Diabetes Journal” (Journal in
Romanian for patients with diabetes and diabetes educators).
Publishing house: Kirchheim, Mainz, Germany.

Co-Editor-in-Chief of the “Diabet, Nutritie, Risc
Cardiometabolic- Diabetes, Metabolism and the Heart”
(Romanian Journal for diabetologists and cardiologists).
Publishing house: Kirchheim, Mainz, Germany.

Member of the Scientific Board of the “Gesellschaft für
Biofaktoren e.V.”

Member of the Board of Directors of the Federation of
International Danube-Symposia for Diabetes mellitus – The
Central-European Association (www.fid.at).

Editor-in-Chief of a website for medical professionals (bilingual:
German-Romanian): www.drdv.de.

BENFOTIAMINE IN THE TREATMENT OF DIABETIC COMPLICATIONS

Beyond improving blood glucose control, pathogenetically oriented treatments of diabetic complications are scarce with benfotiamine and alpha lipoic acid being the only two widely available substances.

Thiamine is an important cofactor of enzymes involved in the glucose metabolism and a marked thiamine deficiency exists in patients with diabetes mellitus. Benfotiamine is a vitamin B1 prodrug with a superior bioavailability compared to thiamine hydrochloride, therefore being preferred when high therapeutic doses are required. It has been shown to reverse 4 hyperglycemia-induced pathomechanisms and to exert antioxidant effects. Clinical studies have demonstrated the efficacy of benfotiamine in the treatment of diabetic neuropathy with an excellent safety profile and preliminary data suggest also beneficial vascular effects.



Karlheinz REINERS

Prof. Dr. med.

Past Vice-Chairman, Department of Neurology,
University Hospital Würzburg, Germany

1969 - 1975: Düsseldorf University Medical School
1975: M.D. (Dept. of Physiological Chemistry, Düsseldorf, Germany)
1976 - 1977: Military Service and Flight Surgeon, German Air Force
1978 - 1982: Specialty training (Neurology) at the Department
of Neurology, Heinrich Heine University, Düsseldorf; Experimental
work on tremor and motor unit discharge behaviour.

Special training in clinical neurophysiology.

1982: Training in psychiatry, University of Düsseldorf

09/01/1982: Board examination as neurologist

1983-1984: Research fellow (Wellcome Foundation) with

Professor R.W. Gilliatt, Department of Clinical Neurology, The
National Hospital for Nervous Diseases, Queen Square, London,
England from 1984 Senior Physician, Department of Neurology,
Heinrich Heine University, Düsseldorf. Experimental research on
peripheral nerve regeneration, axoplasmic transport,

mechanisms of paresis in neuropathies. Clinical studies in

Parkinson's disease and extrapyramidal disorders

2012: Special qualification in Traffic medicine

Academic Appointments: 1989 Assistant Professor of Neurology,
University of Düsseldorf; 1992 - 2016 Full Professor of Neurology
and Vice-Chairman, University Hospital Würzburg, Department of
Neurology; Head, Clinical Neurophysiology Laboratory

Awards: 1990 Myopathy Award, German Muscular Dystrophy
Association; 2005 CME Award, German Ass. for Clinical.

Neurophysiology and Functional Imaging; 2016 Honorary

Award, German Society for Muscle Diseases, Sect. Bavaria

Member of the Editorial Board of the Journal of Neurology

(2001-2006); Member of the Advisory Board of the Journal of

Neural Transmission (2001-2006); Member of the Advisory

Board of Klinische Neurophysiologie (from 2003)

Memberships: DGN - German Neurological Society; DGKN -

German Society of Clinical Neurophysiology (Chairman CME

«Richard-Jung-Kolleg» 2000-2005); DGSS - German Pain

Society; NWG - German Society for Neuroscience; ENA -

European Neurological Association; MDS - Movement Disorder

Society; RSM - Royal Society of Medicine, London (Fellow);

QSAA - Queen Square Alumnus Association, London; AAS -

American Autonomic Association

VITAMIN B12 IN NEUROLOGICAL DISORDERS

Vitamin B12 (Cobalamin) is an essential biofactor for the maturation of red blood cells and all parts of the human nervous system. While most of the compound is protein-bound and inactive, Holo-Trans-Cobalamin (HoloTC) serves as the biologically active form. A severe deficiency would only occur if demand is much increased or stores in liver and muscles have become low, and supply and resorption have become out of balance over months. Most deficiency states occur in the age group over 50 years and result from insufficient intestinal absorption either due to low cleavage from food in subacidic stomach environment, the lack of intrinsic factor or utilization interference from drugs like metformin. In the younger age group, supply may be insufficient owing to restrictive vegetarian or vegan diets. Pregnant and breastfeeding women require a higher supply that is often not provided.

Vitamin B12 deficiency produces a variety of symptoms that are unspecific so that the diagnosis is unfortunately too often missed. It is important to recognize the typical pattern of vitamin B12 deficiency consisting of hematological, neurological and psychiatric features. On the hematological side, a hyperchromic anemia may develop that leads to early tiredness and fatigue even with normal activities. Neurologically, the most severe symptoms result from a conduction deficit in the dorsal column tracts of the spinal cord, leading to unsteadiness of standing and gait, ataxia, and strange sensory deficits, typically felt as a 'tight cuff' around the ankles, but also 'burning feet' sensations. In addition, a peripheral mostly sensory neuropathy may develop causing tingling and numbness of the feet. On the psychological side, a deficiency of vitamin B12 is often involved in the loss of emotional and cognitive drive, concentration and memory deficits, depressive mood swings and premature decline of general intellectual function. In recent years, B12 supplementation has been identified as one of the rare treatments counteracting age-related brain involution and cognitive decline.

While traditionally supplementation of vitamin B12 could only be efficiently provided by intramuscular or subcutaneous injections, recent research has proven that a high-dose oral supplementation using 1.000 µg per day is equally effective in reaching normal serum levels and reversing hematological and neuro-psychiatric symptoms. This is not only good news for patients who are unable to receive injections because of anticoagulant therapy but also provides an easy, safe and cost-effective way of treatment for all patients in need for vitamin B12 supplementation.



Gabriel-Ioan PRADA

MD. PhD

Graduated medical school at “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania in 1984 and after two years of internship at “Fundeni” Clinical Hospital in Bucharest, started his activity in 1986 at the “Ana Aslan” National Institute of Gerontology and Geriatrics in Bucharest.

He is senior specialist in Geriatric Medicine and Gerontology and also in Internal Medicine. Prof. Dr. Prada has a Diploma in Gerontology at the International Institute on Ageing - United Nations and a Master of Science Degree from the Faculty of Medicine, Department of Geriatric Medicine, “Victoria” University of Manchester, United Kingdom under the supervision of Prof. Raymond Tallis, editor of Brocklehurst’s Textbook of Geriatric Medicine and Gerontology. He also has a PhD in Medical Sciences from the “Carol Davila” University of Medicine and Pharmacy, Bucharest.

Currently, Prof. Dr. Prada is Medical Director at the “Ana Aslan” National Institute of Gerontology and Geriatrics and also Professor of Geriatrics and Gerontology, head of the Chair of Geriatrics and Gerontology, Department 5, Faculty of Medicine, “Carol Davila” University of Medicine and Pharmacy, Bucharest. He is author of 13 books and book-chapters, national and international editions, and over 350 papers published or presented at national and international scientific meetings. He has been involved in several international and national research projects, including HYVET (Hypertension in the Very Elderly Trial), PREDICT (Increasing the PaRticipation of the ELderly in Clinical Trials), ERA-AGE 2 (European Research Area in Ageing) and FUTURAGE - A Roadmap for Ageing. He is also full member of the Boards of UEMS-Geriatric Medicine Section (European Union of Medical Specialists), EUGMS (European Union of Geriatric Medicine Societies), IAGG (International Association of Gerontology and Geriatrics) and IAGG-ER Clinical Section.

VITAMINS IN METABOLIC DISEASES AND GERIATRICS

Over the last decades mankind has witnessed an intense phenomenon of demographic aging. Percentage of older people in total population increased steadily in all countries including Romania. Metabolic disorders and especially diabetes mellitus are very often encountered in older people. Diabetes is a huge and growing problem worldwide presenting a 55% increase within the next 20 years and its prevalence increases with age. Vitamins are very important for metabolic diseases in older people.

Vitamin D deficiency increases the risk of metabolic syndrome and type 2 diabetes mellitus. Subclinical B-vitamins deficiencies are not uncommon in older people. Peripheral neuropathy, present in 70% of older diabetics, increases the risk of falls and fractures and negatively affects rehabilitation. Correction of thiamine deficiency in experimental diabetes by high dose therapy with thiamine and also with thiamine monophosphate prodrug, Benfotiamine, prevents the development of incipient diabetic nephropathy, neuropathy and retinopathy. Since 94% of common water-soluble vitamin B1 fails to reach its target, a better alternative is lipid-soluble Benfotiamine since it has a better absorption (almost 7 times more than thiamine) and higher bioavailability, several pharmacokinetic parameters demonstrating superiority over thiamine: higher peak plasma concentration and erythrocyte concentration, superior tissue persistence and lower time to reaching maximum concentration. Therapeutic effect of Benfotiamine occurs almost twice faster than thiamine. Benfotiamine accelerates the healing of diabetic wounds, blocks three major pathways of hyperglycemic damage and prevents experimental diabetic retinopathy. Benfotiamine has both preventive and therapeutic effects in complications of diabetes mellitus in older people.

